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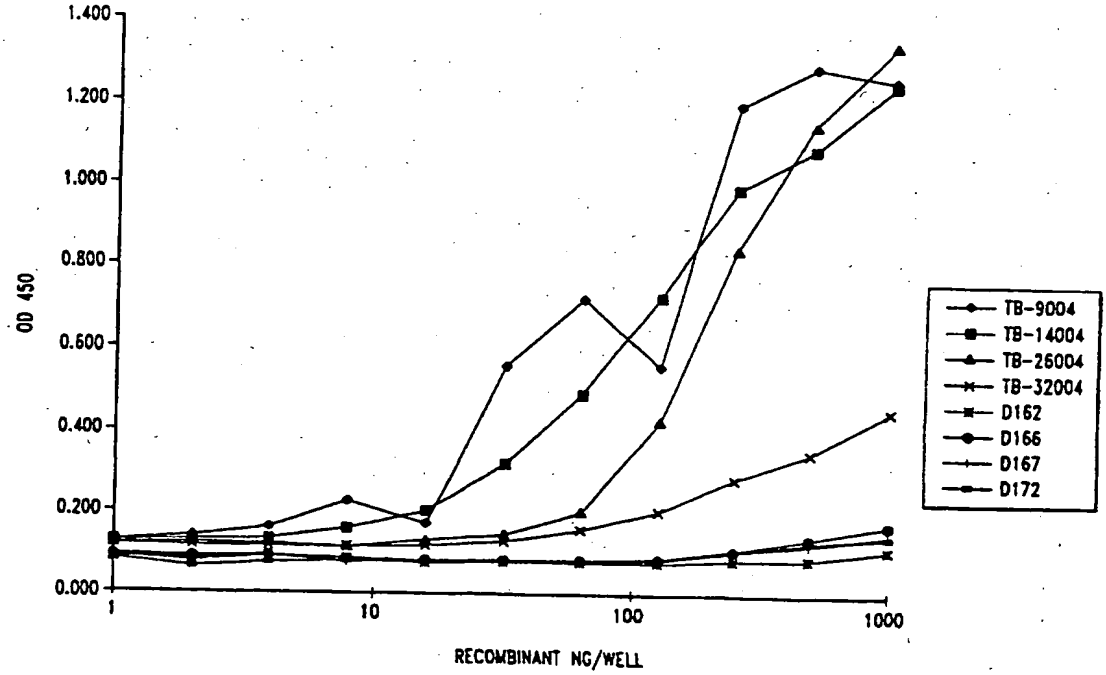

(57) Abstract

Compounds and methods for diagnosing tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one antigenic portion of one or more *M. tuberculosis* secretory or non-secretory proteins, and DNA sequences encoding such polypeptides. Diagnostic kits containing such polypeptides or DNA sequences and a suitable detection reagent may be used for the detection of *M. tuberculosis* infection in patients and biological samples. Antibodies directed against such polypeptides are also provided.

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Description

COMPOUNDS AND METHODS FOR DIAGNOSIS OF TUBERCULOSIS

Technical Field

The present invention relates generally to the detection of *Mycobacterium tuberculosis* infection. The invention is more particularly related to polypeptides comprising a *Mycobacterium tuberculosis* antigen, or a portion or other variant thereof, and the use of such polypeptides for the serodiagnosis of *Mycobacterium tuberculosis* infection.

Background of the Invention

Tuberculosis is a chronic, infectious disease, that is generally caused by infection with *Mycobacterium tuberculosis*. It is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about 8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly manifested as an acute inflammation of the lungs, resulting in fever and a nonproductive cough. If left untreated, serious complications and death typically result.

Although tuberculosis can generally be controlled using extended antibiotic therapy, such treatment is not sufficient to prevent the spread of the disease. Infected individuals may be asymptomatic, but contagious, for some time. In addition,

although compliance with the treatment regimen is critical, patient behavior is difficult to monitor. Some patients do not complete the course of treatment, which can lead to ineffective treatment and the development of drug resistance.

Inhibiting the spread of tuberculosis will require effective vaccination and accurate, early diagnosis of the disease. Currently, vaccination with live bacteria is the most efficient method for inducing protective immunity. The most common Mycobacterium for this purpose is Bacillus Calmette-Guerin (BCG), an avirulent strain of *Mycobacterium bovis*. However, the safety and efficacy of BCG is a source of controversy and some countries, such as the United States, do not vaccinate the general public. Diagnosis is commonly achieved using a skin test, which involves intradermal exposure to tuberculin PPD (protein-purified derivative). Antigen-specific T cell responses result in measurable incubation at the injection site by 48-72 hours after injection, which indicates exposure to Mycobacterial antigens. Sensitivity and specificity have, however, been a problem with this test, and individuals vaccinated with BCG cannot be distinguished from infected individuals.

While macrophages have been shown to act as the principal effectors of *M. tuberculosis* immunity, T cells are the predominant inducers of such immunity. The essential role of T cells in protection against *M. tuberculosis* infection is illustrated by the frequent occurrence of *M. tuberculosis* in AIDS patients, due to the depletion of CD4 T cells associated with human immunodeficiency virus (HIV) infection. Mycobacterium-reactive CD4 T cells have been shown to be potent producers of gamma-interferon (IFN-γ), which, in turn, has been shown to trigger the anti-mycobacterial effects of macrophages in mice. While the role of IFN-γ in humans is less clear, studies have shown that 1,25-dihydroxy-vitamin D3, either alone or in combination with IFN-γ or tumor necrosis factor-alpha, activates human macrophages to inhibit *M. tuberculosis* infection. Furthermore, it is known that IFN-γ stimulates human macrophages to make 1,25-dihydroxy-vitamin D3. Similarly, IL-12 has been shown to play a role in stimulating resistance to *M. tuberculosis* infection. For a review of the immunology of *M. tuberculosis* infection *see* Chan and Kaufmann, in

Tuberculosis: Pathogenesis, Protection and Control, Bloom (ed.), ASM Press, Washington, DC, 1994.

Accordingly, there is a need in the art for improved diagnostic methods for detecting tuberculosis. The present invention fulfills this need and further provides other related advantages.

Summary of the Invention

Briefly stated, the present invention provides compositions and methods for diagnosing tuberculosis. In one aspect, polypeptides are provided comprising an antigenic portion of a soluble *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In one embodiment of this aspect, the soluble antigen has one of the following N-terminal sequences:

(a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 115);

(b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 116);

(c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 117);

(d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro (SEQ ID No. 118);

(e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val (SEQ ID No. 119);

(f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 120);

(g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser (SEQ ID No. 121);

(h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 122);

(i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn (SEQ ID No. 123);

(j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 129)

(k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 130) or

(l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131)

wherein Xaa may be any amino acid.

In a related aspect, polypeptides are provided comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, the antigen having one of the following N-terminal sequences:

(m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132) or

(n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 124)

wherein Xaa may be any amino acid.

In another embodiment, the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96 or a complement thereof under moderately stringent conditions.

In a related aspect, the polypeptides comprise an antigenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, wherein the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the

sequences recited in SEQ ID Nos. 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 26-51 or a complement thereof under moderately stringent conditions.

In related aspects, DNA sequences encoding the above polypeptides, recombinant expression vectors comprising these DNA sequences and host cells transformed or transfected with such expression vectors are also provided.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known *M. tuberculosis* antigen.

In further aspects of the subject invention, methods and diagnostic kits are provided for detecting tuberculosis in a patient. The methods comprise: (a) contacting a biological sample with at least one of the above polypeptides; and (b) detecting in the sample the presence of antibodies that bind to the polypeptide or polypeptides, thereby detecting *M. tuberculosis* infection in the biological sample. Suitable biological samples include whole blood, sputum, serum, plasma, saliva, cerebrospinal fluid and urine. The diagnostic kits comprise one or more of the above polypeptides in combination with a detection reagent.

The present invention also provides methods for detecting *M. tuberculosis* infection comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, the first and the second oligonucleotide primers comprising at least about 10 contiguous nucleotides of a DNA sequence encoding the above polypeptides; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers.

In a further aspect, the present invention provides a method for detecting *M. tuberculosis* infection in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe comprising at least about 15 contiguous nucleotides of a DNA sequence encoding the above polypeptides; and (c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe.

In yet another aspect, the present invention provides antibodies, both polyclonal and monoclonal, that bind to the polypeptides described above, as well as methods for their use in the detection of *M. tuberculosis* infection.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

Brief Description of the Drawings and Sequence Identifiers

Figure 1A and B illustrate the stimulation of proliferation and interferon-γ production in T cells derived from a first and a second *M. tuberculosis*-immune donor, respectively, by the 14 Kd, 20 Kd and 26 Kd antigens described in Example 1.

Figure 2 illustrates the reactivity of two representative polypeptides with sera from *M. tuberculosis*-infected and uninfected individuals, as compared to the reactivity of bacterial lysate.

Figure 3 shows the reactivity of four representative polypeptides with sera from *M. tuberculosis*-infected and uninfected individuals, as compared to the reactivity of the 38 kD antigen.

Figure 4 shows the reactivity of recombinant 38 kD and TbRa11 antigens with sera from *M. tuberculosis* patients, PPD positive donors and normal donors.

Figure 5 shows the reactivity of the antigen TbRa2A with 38 kD negative sera.

Figure 6 shows the reactivity of the antigen of SEQ ID No. 60 with sera from *M. tuberculosis* patients and normal donors.

SEQ. ID NO. 1 is the DNA sequence of TbRa1.
SEQ. ID NO. 2 is the DNA sequence of TbRa10.
SEQ. ID NO. 3 is the DNA sequence of TbRa11.
SEQ. ID NO. 4 is the DNA sequence of TbRa12.
SEQ. ID NO. 5 is the DNA sequence of TbRa13.
SEQ. ID NO. 6 is the DNA sequence of TbRa16.

SEQ. ID NO. 7 is the DNA sequence of TbRa17.
SEQ. ID NO. 8 is the DNA sequence of TbRa18.
SEQ. ID NO. 9 is the DNA sequence of TbRa19.
SEQ. ID NO. 10 is the DNA sequence of TbRa24.
SEQ. ID NO. 11 is the DNA sequence of TbRa26.
SEQ. ID NO. 12 is the DNA sequence of TbRa28.
SEQ. ID NO. 13 is the DNA sequence of TbRa29.
SEQ. ID NO. 14 is the DNA sequence of TbRa2A.
SEQ. ID NO. 15 is the DNA sequence of TbRa3.
SEQ. ID NO. 16 is the DNA sequence of TbRa32.
SEQ. ID NO. 17 is the DNA sequence of TbRa35.
SEQ. ID NO. 18 is the DNA sequence of TbRa36.
SEQ. ID NO. 19 is the DNA sequence of TbRa4.
SEQ. ID NO. 20 is the DNA sequence of TbRa9.
SEQ. ID NO. 21 is the DNA sequence of TbRaB.
SEQ. ID NO. 22 is the DNA sequence of TbRaC.
SEQ. ID NO. 23 is the DNA sequence of TbRaD.
SEQ. ID NO. 24 is the DNA sequence of YYWCPG.
SEQ. ID NO. 25 is the DNA sequence of AAMK.
SEQ. ID NO. 26 is the DNA sequence of TbL-23.
SEQ. ID NO. 27 is the DNA sequence of TbL-24.
SEQ. ID NO. 28 is the DNA sequence of TbL-25.
SEQ. ID NO. 29 is the DNA sequence of TbL-28.
SEQ. ID NO. 30 is the DNA sequence of TbL-29.
SEQ. ID NO. 31 is the DNA sequence of TbH-5.
SEQ. ID NO. 32 is the DNA sequence of TbH-8.
SEQ. ID NO. 33 is the DNA sequence of TbH-9.
SEQ. ID NO. 34 is the DNA sequence of TbM-1.
SEQ. ID NO. 35 is the DNA sequence of TbM-3.
SEQ. ID NO. 36 is the DNA sequence of TbM-6.
SEQ. ID NO. 37 is the DNA sequence of TbM-7.
SEQ. ID NO. 38 is the DNA sequence of TbM-9.
SEQ. ID NO. 39 is the DNA sequence of TbM-12.
SEQ. ID NO. 40 is the DNA sequence of TbM-13.
SEQ. ID NO. 41 is the DNA sequence of TbM-14.
SEQ. ID NO. 42 is the DNA sequence of TbM-15.

SEQ. ID NO. 43 is the DNA sequence of TbH-4.
SEQ. ID NO. 44 is the DNA sequence of TbH-4-FWD.
SEQ. ID NO. 45 is the DNA sequence of TbH-12.
SEQ. ID NO. 46 is the DNA sequence of Tb38-1.
SEQ. ID NO. 47 is the DNA sequence of Tb38-4.
SEQ. ID NO. 48 is the DNA sequence of TbL-17.
SEQ. ID NO. 49 is the DNA sequence of TbL-20.
SEQ. ID NO. 50 is the DNA sequence of TbL-21.
SEQ. ID NO. 51 is the DNA sequence of TbH-16.
SEQ. ID NO. 52 is the DNA sequence of DPEP.
SEQ. ID NO. 53 is the deduced amino acid sequence of DPEP.
SEQ. ID NO. 54 is the protein sequence of DPV N-terminal Antigen.
SEQ. ID NO. 55 is the protein sequence of AVGS N-terminal Antigen.
SEQ. ID NO. 56 is the protein sequence of AAMK N-terminal Antigen.
SEQ. ID NO. 57 is the protein sequence of YYWC N-terminal Antigen.
SEQ. ID NO. 58 is the protein sequence of DIGS N-terminal Antigen.
SEQ. ID NO. 59 is the protein sequence of AEES N-terminal Antigen.
SEQ. ID NO. 60 is the protein sequence of DPEP N-terminal Antigen.
SEQ. ID NO. 61 is the protein sequence of APKT N-terminal Antigen.
SEQ. ID NO. 62 is the protein sequence of DPAS N-terminal Antigen.
SEQ. ID NO. 63 is the deduced amino acid sequence of TbM-1 Peptide.
SEQ. ID NO. 64 is the deduced amino acid sequence of TbRa1.
SEQ. ID NO. 65 is the deduced amino acid sequence of TbRa10.
SEQ. ID NO. 66 is the deduced amino acid sequence of TbRa11.
SEQ. ID NO. 67 is the deduced amino acid sequence of TbRa12.
SEQ. ID NO. 68 is the deduced amino acid sequence of TbRa13.
SEQ. ID NO. 69 is the deduced amino acid sequence of TbRa16.
SEQ. ID NO. 70 is the deduced amino acid sequence of TbRa17.
SEQ. ID NO. 71 is the deduced amino acid sequence of TbRa18.
SEQ. ID NO. 72 is the deduced amino acid sequence of TbRa19.
SEQ. ID NO. 73 is the deduced amino acid sequence of TbRa24.
SEQ. ID NO. 74 is the deduced amino acid sequence of TbRa26.
SEQ. ID NO. 75 is the deduced amino acid sequence of TbRa28.
SEQ. ID NO. 76 is the deduced amino acid sequence of TbRa29.
SEQ. ID NO. 77 is the deduced amino acid sequence of TbRa2A.
SEQ. ID NO. 78 is the deduced amino acid sequence of TbRa3.

SEQ. ID NO. 79 is the deduced amino acid sequence of TbRa32.
SEQ. ID NO. 80 is the deduced amino acid sequence of TbRa35.
SEQ. ID NO. 81 is the deduced amino acid sequence of TbRa36.
SEQ. ID NO. 82 is the deduced amino acid sequence of TbRa4.
SEQ. ID NO. 83 is the deduced amino acid sequence of TbRa9.
SEQ. ID NO. 84 is the deduced amino acid sequence of TbRaB.
SEQ. ID NO. 85 is the deduced amino acid sequence of TbRaC.
SEQ. ID NO. 86 is the deduced amino acid sequence of TbRaD.
SEQ. ID NO. 87 is the deduced amino acid sequence of YYWCPG.
SEQ. ID NO. 88 is the deduced amino acid sequence of TbAAMK.
SEQ. ID NO. 89 is the deduced amino acid sequence of Tb38-1.
SEQ. ID NO. 90 is the deduced amino acid sequence of TbH-4.
SEQ. ID NO. 91 is the deduced amino acid sequence of TbH-8.
SEQ. ID NO. 92 is the deduced amino acid sequence of TbH-9.
SEQ. ID NO. 93 is the deduced amino acid sequence of TbH-12.
SEQ. ID NO. 94 is the DNA sequence of DPAS.
SEQ. ID NO. 95 is the deduced amino acid sequence of DPAS.
SEQ. ID NO. 96 is the DNA sequence of DPV.
SEQ. ID NO. 97 is the deduced amino acid sequence of DPV.
SEQ. ID NO. 98 is the DNA sequence of ESAT-6.
SEQ. ID NO. 99 is the deduced amino acid sequence of ESAT-6.
SEQ. ID NO. 100 is the DNA sequence of TbH-8-2.
SEQ. ID NO. 101 is the DNA sequence of TbH-9FL.
SEQ. ID NO. 102 is the deduced amino acid sequence of TbH-9FL.
SEQ. ID NO. 103 is the DNA sequence of TbH-9-1.
SEQ. ID NO. 104 is the deduced amino acid sequence of TbH-9-1.
SEQ. ID NO. 105 is the DNA sequence of TbH-9-4.
SEQ. ID NO. 106 is the deduced amino acid sequence of TbH-9-4.
SEQ. ID NO. 107 is the DNA sequence of Tb38-1F2 IN.
SEQ. ID NO. 108 is the DNA sequence of Tb38-1F2 RP.
SEQ. ID NO. 109 is the deduced amino acid sequence of Tb37-FL.
SEQ. ID NO. 110 is the deduced amino acid sequence of Tb38-IN.
SEQ. ID NO. 111 is the DNA sequence of Tb38-1F3.
SEQ. ID NO. 112 is the deduced amino acid sequence of Tb38-1F3.
SEQ. ID NO. 113 is the DNA sequence of Tb38-1F5.
SEQ. ID NO. 114 is the DNA sequence of Tb38-1F6.

SEQ. ID NO. 115 is the deduced N-terminal amino acid sequence of DPV.
SEQ. ID NO. 116 is the deduced N-terminal amino acid sequence of AVGS.
SEQ. ID NO. 117 is the deduced N-terminal amino acid sequence of AAMK.
SEQ. ID NO. 118 is the deduced N-terminal amino acid sequence of YYWC.
SEQ. ID NO. 119 is the deduced N-terminal amino acid sequence of DIGS.
SEQ. ID NO. 120 is the deduced N-terminal amino acid sequence of AAES.
SEQ. ID NO. 121 is the deduced N-terminal amino acid sequence of DPEP.
SEQ. ID NO. 122 is the deduced N-terminal amino acid sequence of APKT.
SEQ. ID NO. 123 is the deduced N-terminal amino acid sequence of DPAS.
SEQ. ID NO. 124 is the protein sequence of DPPD N-terminal Antigen.
SEQ ID NO. 125-128 are the protein sequences of four DPPD cyanogen bromide fragments.
SEQ ID NO. 129 is the N-terminal protein sequence of XDS antigen.
SEQ ID NO. 130 is the N-terminal protein sequence of AGD antigen.
SEQ ID NO. 131 is the N-terminal protein sequence of APE antigen.
SEQ ID NO. 132 is the N-terminal protein sequence of XYI antigen.

Detailed Description of the Invention

As noted above, the present invention is generally directed to compositions and methods for diagnosing tuberculosis. The compositions of the subject invention include polypeptides that comprise at least one antigenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. Polypeptides within the scope of the present invention include, but are not limited to, soluble *M. tuberculosis* antigens. A "soluble *M. tuberculosis* antigen" is a protein of *M. tuberculosis* origin that is present in *M. tuberculosis* culture filtrate. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising an antigenic portion of one of the above antigens may consist entirely of the antigenic portion, or may contain additional sequences. The additional sequences may be derived from the native *M. tuberculosis* antigen or may be heterologous, and such sequences may (but need not) be antigenic.

An "antigenic portion" of an antigen (which may or may not be soluble) is a portion that is capable of reacting with sera obtained from an *M. tuberculosis*-infected individual (*i.e.*, generates an absorbance reading with sera from infected individuals that is at least three standard deviations above the absorbance obtained with sera from uninfected individuals, in a representative ELISA assay described herein). An "*M. tuberculosis*-infected individual" is a human who has been infected with *M. tuberculosis* (*e.g.*, has an intradermal skin test response to PPD that is at least 0.5 cm in diameter). Infected individuals may display symptoms of tuberculosis or may be free of disease symptoms. Polypeptides comprising at least an antigenic portion of one or more *M. tuberculosis* antigens as described herein may generally be used, alone or in combination, to detect tuberculosis in a patient.

The compositions and methods of this invention also encompass variants of the above polypeptides. A "variant," as used herein, is a polypeptide that differs from the native antigen only in conservative substitutions and/or modifications, such that the antigenic properties of the polypeptide are retained. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein.

A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the

protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

In a related aspect, combination polypeptides are disclosed. A "combination polypeptide" is a polypeptide comprising at least one of the above antigenic portions and one or more additional antigenic *M. tuberculosis* sequences, which are joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly (*i.e.*, with no intervening amino acids) or may be joined by way of a linker sequence (*e.g.*, Gly-Cys-Gly) that does not significantly diminish the antigenic properties of the component polypeptides.

In general, *M. tuberculosis* antigens, and DNA sequences encoding such antigens, may be prepared using any of a variety of procedures. For example, soluble antigens may be isolated from *M. tuberculosis* culture filtrate by procedures known to those of ordinary skill in the art, including anion-exchange and reverse phase chromatography. Purified antigens may then be evaluated for a desired property, such as the ability to react with sera obtained from an *M. tuberculosis*-infected individual. Such screens may be performed using the representative methods described herein. Antigens may then be partially sequenced using, for example, traditional Edman chemistry. *See* Edman and Berg, *Eur. J. Biochem. 80*:116-132, 1967.

Antigens may also be produced recombinantly using a DNA sequence that encodes the antigen, which has been inserted into an expression vector and expressed in an appropriate host. DNA molecules encoding soluble antigens may be isolated by screening an appropriate *M. tuberculosis* expression library with anti-sera (*e.g.*, rabbit) raised specifically against soluble *M. tuberculosis* antigens. DNA sequences encoding antigens that may or may not be soluble may be identified by screening an appropriate *M. tuberculosis* genomic or cDNA expression library with sera obtained from patients infected with *M. tuberculosis*. Such screens may generally be performed using techniques well known in the art, such as those described in Sambrook

et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989.

DNA sequences encoding soluble antigens may also be obtained by screening an appropriate *M. tuberculosis* cDNA or genomic DNA library for DNA sequences that hybridize to degenerate oligonucleotides derived from partial amino acid sequences of isolated soluble antigens. Degenerate oligonucleotide sequences for use in such a screen may be designed and synthesized, and the screen may be performed, as described (for example) in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY (and references cited therein). Polymerase chain reaction (PCR) may also be employed, using the above oligonucleotides in methods well known in the art, to isolate a nucleic acid probe from a cDNA or genomic library. The library screen may then be performed using the isolated probe.

Regardless of the method of preparation, the antigens described herein are "antigenic." More specifically, the antigens have the ability to react with sera obtained from an *M. tuberculosis*-infected individual. Reactivity may be evaluated using, for example, the representative ELISA assays described herein, where an absorbance reading with sera from infected individuals that is at least three standard deviations above the absorbance obtained with sera from uninfected individuals is considered positive.

Antigenic portions of *M. tuberculosis* antigens may be prepared and identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3d ed., Raven Press, 1993, pp. 243-247 and references cited therein. Such techniques include screening polypeptide portions of the native antigen for antigenic properties. The representative ELISAs described herein may generally be employed in these screens. An antigenic portion of a polypeptide is a portion that, within such representative assays, generates a signal in such assays that is substantially similar to that generated by the full length antigen. In other words, an antigenic portion of a *M. tuberculosis* antigen generates at least about 20%, and preferably about 100%, of the signal induced by the full length antigen in a model ELISA as described herein.

Portions and other variants of *M. tuberculosis* antigens may be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc., Foster City, CA, and may be operated according to the manufacturer's instructions. Variants of a native antigen may generally be prepared using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis. Sections of the DNA sequence may also be removed using standard techniques to permit preparation of truncated polypeptides.

Recombinant polypeptides containing portions and/or variants of a native antigen may be readily prepared from a DNA sequence encoding the polypeptide using a variety of techniques well known to those of ordinary skill in the art. For example, supernatants from suitable host/vector systems which secrete recombinant protein into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant protein.

Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides as described herein. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as COS or CHO. The DNA sequences expressed in this manner may

encode naturally occurring antigens, portions of naturally occurring antigens, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in substantially pure form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure and most preferably at least about 99% pure. For use in the methods described herein, however, such substantially pure polypeptides may be combined.

In certain specific embodiments, the subject invention discloses polypeptides comprising at least an antigenic portion of a soluble *M. tuberculosis* antigen (or a variant of such an antigen), where the antigen has one of the following N-terminal sequences:

(a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 115);

(b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 116);

(c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 117);

(d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro (SEQ ID No. 118);

(e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val (SEQ ID No. 119);

(f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 120);

(g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser (SEQ ID No. 121);

(h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 122);

(i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Gln-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn (SEQ ID No. 123);

(j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 129)

(k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 130) or

(l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131)

wherein Xaa may be any amino acid, preferably a cysteine residue. A DNA sequence encoding the antigen identified as (g) above is provided in SEQ ID No. 52, the deduced amino acid sequence of which is provided in SEQ ID No. 53. A DNA sequence encoding the antigen identified as (a) above is provided in SEQ ID No. 96; its deduced amino acid sequence is provided in SEQ ID No. 97. A DNA sequence corresponding to antigen (d) above is provided in SEQ ID No. 24, a DNA sequence corresponding to antigen (c) is provided in SEQ ID No. 25 and a DNA sequence corresponding to antigen (I) is disclosed in SEQ ID No. 94 and its deduced amino acid sequence is provided in SEQ ID No. 95.

In a further specific embodiment, the subject invention discloses polypeptides comprising at least an immunogenic portion of an *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

(m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132) or

(n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 124)

wherein Xaa may be any amino acid, preferably a cysteine residue.

In other specific embodiments, the subject invention discloses polypeptides comprising at least an antigenic portion of a soluble *M. tuberculosis* antigen (or a variant of such an antigen) that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94

and 96, (b) the complements of such DNA sequences, or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

In further specific embodiments, the subject invention discloses polypeptides comprising at least an antigenic portion of a *M. tuberculosis* antigen (or a variant of such an antigen), which may or may not be soluble, that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos. 26-51, (b) the complements of such DNA sequences or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

In the specific embodiments discussed above, the *M. tuberculosis* antigens include variants that are encoded DNA sequences which are substantially homologous to one or more of DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known *M. tuberculosis* antigen, such as the 38 kD antigen described above or ESAT-6 (SEQ ID Nos. 98 and 99), together with variants of such fusion proteins. The fusion proteins of the present invention may also include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or

without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8562, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric hindrance.

In another aspect, the present invention provides methods for using the polypeptides described above to diagnose tuberculosis. In this aspect, methods are provided for detecting *M. tuberculosis* infection in a biological sample, using one or more of the above polypeptides, alone or in combination. In embodiments in which multiple polypeptides are employed, polypeptides other than those specifically described herein, such as the 38 kD antigen described in Andersen and Hansen, *Infect. Immun. 57*:2481-2488, 1989, may be included. As used herein, a "biological sample" is any antibody-containing sample obtained from a patient. Preferably, the sample is whole blood, sputum, serum, plasma, saliva, cerebrospinal fluid or urine. More

preferably, the sample is a blood, serum or plasma sample obtained from a patient or a blood supply. The polypeptide(s) are used in an assay, as described below, to determine the presence or absence of antibodies to the polypeptide(s) in the sample, relative to a predetermined cut-off value. The presence of such antibodies indicates previous sensitization to mycobacteria antigens which may be indicative of tuberculosis.

In embodiments in which more than one polypeptide is employed, the polypeptides used are preferably complementary (*i.e.*, one component polypeptide will tend to detect infection in samples where the infection would not be detected by another component polypeptide). Complementary polypeptides may generally be identified by using each polypeptide individually to evaluate serum samples obtained from a series of patients known to be infected with *M. tuberculosis*. After determining which samples test positive (as described below) with each polypeptide, combinations of two or more polypeptides may be formulated that are capable of detecting infection in most, or all, of the samples tested. Such polypeptides are complementary. For example, approximately 25-30% of sera from tuberculosis-infected individuals are negative for antibodies to any single protein, such as the 38 kD antigen mentioned above. Complementary polypeptides may, therefore, be used in combination with the 38 kD antigen to improve sensitivity of a diagnostic test.

There are a variety of assay formats known to those of ordinary skill in the art for using one or more polypeptides to detect antibodies in a sample. *See*, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988, which is incorporated herein by reference. In a preferred embodiment, the assay involves the use of polypeptide immobilized on a solid support to bind to and remove the antibody from the sample. The bound antibody may then be detected using a detection reagent that contains a reporter group. Suitable detection reagents include antibodies that bind to the antibody/polypeptide complex and free polypeptide labeled with a reporter group (*e.g.*, in a semi-competitive assay). Alternatively, a competitive assay may be utilized, in which an antibody that binds to the polypeptide is labeled with a reporter group and allowed to bind to the immobilized antigen after incubation of the antigen with the sample. The extent to which components of the sample inhibit the

binding of the labeled antibody to the polypeptide is indicative of the reactivity of the sample with the immobilized polypeptide.

The solid support may be any solid material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681.

The polypeptides may be bound to the solid support using a variety of techniques known to those of ordinary skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "bound" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Binding by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the polypeptide, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of polypeptide ranging from about 10 ng to about 1 µg, and preferably about 100 ng, is sufficient to bind an adequate amount of antigen.

Covalent attachment of polypeptide to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the polypeptide. For example, the polypeptide may be bound to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the polypeptide (*see*, *e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is an enzyme linked immunosorbent assay (ELISA). This assay may be performed by first contacting a polypeptide antigen that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that antibodies to the polypeptide within the sample are allowed to bind to the immobilized polypeptide. Unbound sample is then removed from the immobilized polypeptide and a detection reagent capable of binding to the immobilized antibody-polypeptide complex is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific detection reagent.

More specifically, once the polypeptide is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO) may be employed. The immobilized polypeptide is then incubated with the sample, and antibody is allowed to bind to the antigen. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of antibody within a *M. tuberculosis*-infected sample. Preferably, the contact time is sufficient to achieve a level of binding that is at least 95% of that achieved at equilibrium between bound and unbound antibody. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. Detection reagent may then be added to the solid support. An appropriate detection reagent is any compound that binds to the immobilized antibody-polypeptide complex and that can be detected by any of a variety of means known to those in the art. Preferably, the detection reagent contains a binding agent (such as, for example, Protein A, Protein G, immunoglobulin, lectin or free antigen) conjugated to a reporter group. Preferred

reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of binding agent to reporter group may be achieved using standard methods known to those of ordinary skill in the art. Common binding agents may also be purchased conjugated to a variety of reporter groups from many commercial sources (*e.g.*, Zymed Laboratories, San Francisco, CA, and Pierce, Rockford, IL).

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound antibody. An appropriate amount of time may generally be determined from the manufacturer's instructions or by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of anti-*M. tuberculosis* antibodies in the sample, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antigen is incubated with samples from an uninfected patient. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for tuberculosis. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, pp. 106-107. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive

rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for tuberculosis.

In a related embodiment, the assay is performed in a rapid flow-through or strip test format, wherein the antigen is immobilized on a membrane, such as nitrocellulose. In the flow-through test, antibodies within the sample bind to the immobilized polypeptide as the sample passes through the membrane. A detection reagent (*e.g.*, protein A-colloidal gold) then binds to the antibody-polypeptide complex as the solution containing the detection reagent flows through the membrane. The detection of bound detection reagent may then be performed as described above. In the strip test format, one end of the membrane to which polypeptide is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing detection reagent and to the area of immobilized polypeptide. Concentration of detection reagent at the polypeptide indicates the presence of anti-*M. tuberculosis* antibodies in the sample. Typically, the concentration of detection reagent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of polypeptide immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of antibodies that would be sufficient to generate a positive signal in an ELISA, as discussed above. Preferably, the amount of polypeptide immobilized on the membrane ranges from about 25 ng to about 1 μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount (*e.g.*, one drop) of patient serum or blood.

Of course, numerous other assay protocols exist that are suitable for use with the polypeptides of the present invention. The above descriptions are intended to be exemplary only.

In yet another aspect, the present invention provides antibodies to the inventive polypeptides. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks,

colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Antibodies may be used in diagnostic tests to detect the presence of *M. tuberculosis* antigens using assays similar to those detailed above and other techniques well known to those of skill in the art, thereby providing a method for detecting *M. tuberculosis* infection in a patient.

Diagnostic reagents of the present invention may also comprise DNA sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, primers comprising at least 10 contiguous oligonucleotides of the subject DNA sequences may be used in polymerase chain reaction (PCR) based tests. Similarly, probes comprising at least 15 contiguous oligonucleotides of the subject DNA sequences may be used for hybridizing to specific sequences. Techniques for both PCR based tests and hybridization tests are well known in the art. Primers or probes may thus be used to detect *M. tuberculosis* infection in biological samples, preferably sputum, blood, serum, saliva, cerebrospinal fluid or urine. DNA probes or primers comprising oligonucleotide sequences described above may be used alone, in combination with each other, or with previously identified sequences, such as the 38 kD antigen discussed above.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

EXAMPLE 1

PURIFICATION AND CHARACTERIZATION OF POLYPEPTIDES FROM *M. TUBERCULOSIS* CULTURE FILTRATE

This example illustrates the preparation of *M. tuberculosis* soluble polypeptides from culture filtrate. Unless otherwise noted, all percentages in the following example are weight per volume.

M. tuberculosis (either H37Ra, ATCC No. 25177, or H37Rv, ATCC No. 25618) was cultured in sterile GAS media at 37°C for fourteen days. The media was then vacuum filtered (leaving the bulk of the cells) through a 0.45 μ filter into a sterile 2.5 L bottle. The media was then filtered through a 0.2 μ filter into a sterile 4 L bottle. NaN_3 was then added to the culture filtrate to a concentration of 0.04%. The bottles were then placed in a 4°C cold room.

The culture filtrate was concentrated by placing the filtrate in a 12 L reservoir that had been autoclaved and feeding the filtrate into a 400 ml Amicon stir cell which had been rinsed with ethanol and contained a 10,000 kDa MWCO membrane. The pressure was maintained at 60 psi using nitrogen gas. This procedure reduced the 12 L volume to approximately 50 ml.

The culture filtrate was then dialyzed into 0.1% ammonium bicarbonate using a 8,000 kDa MWCO cellulose ester membrane, with two changes of ammonium bicarbonate solution. Protein concentration was then determined by a commercially available BCA assay (Pierce, Rockford, IL).

The dialyzed culture filtrate was then lyophilized, and the polypeptides resuspended in distilled water. The polypeptides were then dialyzed against 0.01 mM 1,3 bis[tris(hydroxymethyl)-methylamino]propane, pH 7.5 (Bis-Tris propane buffer), the initial conditions for anion exchange chromatography. Fractionation was performed using gel profusion chromatography on a POROS 146 II Q/M anion exchange column

4.6 mm x 100 mm (Perseptive BioSystems, Framingham, MA) equilibrated in 0.01 mM Bis-Tris propane buffer pH 7.5. Polypeptides were eluted with a linear 0-0.5 M NaCl gradient in the above buffer system. The column eluent was monitored at a wavelength of 220 nm.

The pools of polypeptides eluting from the ion exchange column were dialyzed against distilled water and lyophilized. The resulting material was dissolved in 0.1% trifluoroacetic acid (TFA) pH 1.9 in water, and the polypeptides were purified on a Delta-Pak C18 column (Waters, Milford, MA) 300 Angstrom pore size, 5 micron particle size (3.9 x 150 mm). The polypeptides were eluted from the column with a linear gradient from 0-60% dilution buffer (0.1% TFA in acetonitrile). The flow rate was 0.75 ml/minute and the HPLC eluent was monitored at 214 nm. Fractions containing the eluted polypeptides were collected to maximize the purity of the individual samples. Approximately 200 purified polypeptides were obtained.

The purified polypeptides were then screened for the ability to induce T-cell proliferation in PBMC preparations. The PBMCs from donors known to be PPD skin test positive and whose T cells were shown to proliferate in response to PPD and crude soluble proteins from MTB were cultured in medium comprising RPMI 1640 supplemented with 10% pooled human serum and 50 µg/ml gentamicin. Purified polypeptides were added in duplicate at concentrations of 0.5 to 10 µg/mL. After six days of culture in 96-well round-bottom plates in a volume of 200 µl, 50 µl of medium was removed from each well for determination of IFN-γ levels, as described below. The plates were then pulsed with 1 µCi/well of tritiated thymidine for a further 18 hours, harvested and tritium uptake determined using a gas scintillation counter. Fractions that resulted in proliferation in both replicates three fold greater than the proliferation observed in cells cultured in medium alone were considered positive.

IFN-γ was measured using an enzyme-linked immunosorbent assay (ELISA). ELISA plates were coated with a mouse monoclonal antibody directed to human IFN-γ (Chemicon) in PBS for four hours at room temperature. Wells were then blocked with PBS containing 5% (W/V) non-fat dried milk for 1 hour at room temperature. The plates were then washed six times in PBS/0.2% TWEEN-20 and

samples diluted 1:2 in culture medium in the ELISA plates were incubated overnight at room temperature. The plates were again washed and a polyclonal rabbit anti-human IFN-γ serum diluted 1:3000 in PBS/10% normal goat serum was added to each well. The plates were then incubated for two hours at room temperature, washed and horseradish peroxidase-coupled anti-rabbit IgG (Jackson Labs.) was added at a 1:2000 dilution in PBS/5% non-fat dried milk. After a further two hour incubation at room temperature, the plates were washed and TMB substrate added. The reaction was stopped after 20 min with 1 N sulfuric acid. Optical density was determined at 450 nm using 570 nm as a reference wavelength. Fractions that resulted in both replicates giving an OD two fold greater than the mean OD from cells cultured in medium alone, plus 3 standard deviations, were considered positive.

For sequencing, the polypeptides were individually dried onto Biobrene™ (Perkin Elmer/Applied BioSystems Division, Foster City, CA) treated glass fiber filters. The filters with polypeptide were loaded onto a Perkin Elmer/Applied BioSystems Division Procise 492 protein sequencer. The polypeptides were sequenced from the amino terminal and using traditional Edman chemistry. The amino acid sequence was determined for each polypeptide by comparing the retention time of the PTH amino acid derivative to the appropriate PTH derivative standards.

Using the procedure described above, antigens having the following N-terminal sequences were isolated:

(a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Xaa-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 54);

(b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 55);

(c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 56);

(d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro (SEQ ID No. 57);

(e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val (SEQ ID No. 58);

(f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 59);

(g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ala-Pro-Pro-Ala (SEQ ID No. 60); and

(h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 61);

wherein Xaa may be any amino acid.

An additional antigen was isolated employing a microbore HPLC purification step in addition to the procedure described above. Specifically, 20 µl of a fraction comprising a mixture of antigens from the chromatographic purification step previously described, was purified on an Aquapore C18 column (Perkin Elmer/Applied Biosystems Division, Foster City, CA) with a 7 micron pore size, column size 1 mm x 100 mm, in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted from the column with a linear gradient of 1%/minute of acetonitrile (containing 0.05% TFA) in water (0.05% TFA) at a flow rate of 80 µl/minute. The eluent was monitored at 250 nm. The original fraction was separated into 4 major peaks plus other smaller components and a polypeptide was obtained which was shown to have a molecular weight of 12.054 Kd (by mass spectrometry) and the following N-terminal sequence:

(i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Gln-Thr-Ser-Leu-Leu-Asn-Asn-Leu-Ala-Asp-Pro-Asp-Val-Ser-Phe-Ala-Asp (SEQ ID No. 62).

This polypeptide was shown to induce proliferation and IFN-γ production in PBMC preparations using the assays described above.

Additional soluble antigens were isolated from *M. tuberculosis* culture filtrate as follows. *M. tuberculosis* culture filtrate was prepared as described above. Following dialysis against Bis-Tris propane buffer, at pH 5.5, fractionation was performed using anion exchange chromatography on a Poros QE column 4.6 x 100 mm (Perseptive Biosystems) equilibrated in Bis-Tris propane buffer pH 5.5. Polypeptides

were eluted with a linear 0-1.5 M NaCl gradient in the above buffer system at a flow rate of 10 ml/min. The column eluent was monitored at a wavelength of 214 nm.

The fractions eluting from the ion exchange column were pooled and subjected to reverse phase chromatography using a Poros R2 column 4.6 x 100 mm (Perseptive Biosystems). Polypeptides were eluted from the column with a linear gradient from 0-100% acetonitrile (0.1% TFA) at a flow rate of 5 ml/min. The eluent was monitored at 214 nm.

Fractions containing the eluted polypeptides were lyophilized and resuspended in 80 µl of aqueous 0.1% TFA and further subjected to reverse phase chromatography on a Vydac C4 column 4.6 x 150 mm (Western Analytical, Temecula, CA) with a linear gradient of 0-100% acetonitrile (0.1% TFA) at a flow rate of 2 ml/min. Eluent was monitored at 214 nm.

The fraction with biological activity was separated into one major peak plus other smaller components. Western blot of this peak onto PVDF membrane revealed three major bands of molecular weights 14 Kd, 20 Kd and 26 Kd. These polypeptides were determined to have the following N-terminal sequences, respectively:

(j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 129)

(k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 130) and

(l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131), wherein Xaa may be any amino acid.

Using the assays described above, these polypeptides were shown to induce proliferation and IFN-γ production in PBMC preparations. Figs. 1A and B show the results of such assays using PBMC preparations from a first and a second donor, respectively.

DNA sequences that encode the antigens designated as (a), (c), (d) and (g) above were obtained by screening a *M. tuberculosis* genomic library using ^{32}P end labeled degenerate oligonucleotides corresponding to the N-terminal sequence and containing *M. tuberculosis* codon bias. The screen performed using a probe

corresponding to antigen (a) above identified a clone having the sequence provided in SEQ ID No. 96. The polypeptide encoded by SEQ ID No. 96 is provided in SEQ ID No. 97. The screen performed using a probe corresponding to antigen (g) above identified a clone having the sequence provided in SEQ ID No. 52. The polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. The screen performed using a probe corresponding to antigen (d) above identified a clone having the sequence provided in SEQ ID No. 24, and the screen performed with a probe corresponding to antigen (c) identified a clone having the sequence provided in SEQ ID No. 25.

The above amino acid sequences were compared to known amino acid sequences in the gene bank using the DNA STAR system. The database searched contains some 173,000 proteins and is a combination of the Swiss, PIR databases along with translated protein sequences (Version 87). No significant homologies to the amino acid sequences for antigens (a)-(h) and (l) were detected.

The amino acid sequence for antigen (i) was found to be homologous to a sequence from *M. leprae*. The full length *M. leprae* sequence was amplified from genomic DNA using the sequence obtained from GENBANK. This sequence was then used to screen an *M. tuberculosis* library and a full length copy of the *M. tuberculosis* homologue was obtained (SEQ ID No. 94).

The amino acid sequence for antigen (j) was found to be homologous to a known *M. tuberculosis* protein translated from a DNA sequence. To the best of the inventors' knowledge, this protein has not been previously shown to possess T-cell stimulatory activity. The amino acid sequence for antigen (k) was found to be related to a sequence from *M. leprae*.

In the proliferation and IFN-γ assays described above, using three PPD positive donors, the results for representative antigens provided above are presented in Table 1:

TABLE 1

RESULTS OF PBMC PROLIFERATION AND IFN-γ ASSAYS

Sequence	Proliferation	IFN-γ
(a)	+	-
(c)	+++	+++
(d)	++	++
(g)	+++	+++
(h)	+++	+++

In Table 1, responses that gave a stimulation index (SI) of between 2 and 4 (compared to cells cultured in medium alone) were scored as +, as SI of 4-8 or 2-4 at a concentration of 1 μg or less was scored as ++ and an SI of greater than 8 was scored as +++. The antigen of sequence (i) was found to have a high SI (+++) for one donor and lower SI (++ and +) for the two other donors in both proliferation and IFN-γ assays. These results indicate that these antigens are capable of inducing proliferation and/or interferon-γ production.

EXAMPLE 2

USE OF PATIENT SERA TO ISOLATE *M. TUBERCULOSIS* ANTIGENS

This example illustrates the isolation of antigens from *M. tuberculosis* lysate by screening with serum from *M. tuberculosis*-infected individuals.

Dessicated *M. tuberculosis* H37Ra (Difco Laboratories) was added to a 2% NP40 solution, and alternately homogenized and sonicated three times. The resulting suspension was centrifuged at 13,000 rpm in microfuge tubes and the supernatant put through a 0.2 micron syringe filter. The filtrate was bound to Macro Prep DEAE beads (BioRad, Hercules, CA). The beads were extensively washed with 20 mM Tris pH 7.5 and bound proteins eluted with 1M NaCl. The NaCl elute was dialyzed overnight against 10 mM Tris, pH 7.5. Dialyzed solution was treated with

DNase and RNase at 0.05 mg/ml for 30 min. at room temperature and then with α-D-mannosidase, 0.5 U/mg at pH 4.5 for 3-4 hours at room temperature. After returning to pH 7.5, the material was fractionated via FPLC over a Bio Scale-Q-20 column (BioRad). Fractions were combined into nine pools, concentrated in a Centriprep 10 (Amicon, Beverley, MA) and screened by Western blot for serological activity using a serum pool from *M. tuberculosis*-infected patients which was not immunoreactive with other antigens of the present invention.

The most reactive fraction was run in SDS-PAGE and transferred to PVDF. A band at approximately 85 Kd was cut out yielding the sequence:

(m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132), wherein Xaa may be any amino acid.

Comparison of this sequence with those in the gene bank as described above, revealed no significant homologies to known sequences.

EXAMPLE 3

PREPARATION OF DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

This example illustrates the preparation of DNA sequences encoding *M. tuberculosis* antigens by screening a *M. tuberculosis* expression library with sera obtained from patients infected with *M. tuberculosis*, or with anti-sera raised against *M. tuberculosis* antigens.

A. PREPARATION OF *M. TUBERCULOSIS* SOLUBLE ANTIGENS USING RABBIT ANTI-SERA

Genomic DNA was isolated from the *M. tuberculosis* strain H37Ra. The DNA was randomly sheared and used to construct an expression library using the Lambda ZAP expression system (Stratagene, La Jolla. CA). Rabbit anti-sera was generated against secretory proteins of the *M. tuberculosis* strains H37Ra, H37Rv and Erdman by immunizing a rabbit with concentrated supernatant of the *M. tuberculosis*

cultures. Specifically, the rabbit was first immunized subcutaneously with 200 μg of protein antigen in a total volume of 2 ml containing 100 μg muramyl dipeptide (Calbiochem, La Jolla, CA) and 1 ml of incomplete Freund's adjuvant. Four weeks later the rabbit was boosted subcutaneously with 100 μg antigen in incomplete Freund's adjuvant. Finally, the rabbit was immunized intravenously four weeks later with 50 μg protein antigen. The anti-sera were used to screen the expression library as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 25 represent sequences that have not been previously identified in *M. tuberculosis*. Proteins were induced by IPTG and purified by gel elution, as described in Skeiky et al., *J. Exp. Med. 181*:1527-1537, 1995. Representative partial sequences of DNA molecules identified in this screen are provided in SEQ ID Nos. 1-25. The corresponding predicted amino acid sequences are shown in SEQ ID Nos. 64-88.

On comparison of these sequences with known sequences in the gene bank using the databases described above, it was found that the clones referred to hereinafter as TbRA2A, TbRA16, TbRA18, and TbRA29 (SEQ ID Nos. 77, 69, 71, 76) show some homology to sequences previously identified in *Mycobacterium leprae* but not in *M. tuberculosis*. TbRA11, TbRA26, TbRA28 and TbDPEP (SEQ ID Nos. 66, 74, 75, 53) have been previously identified in *M. tuberculosis*. No significant homologies were found to TbRA1, TbRA3, TbRA4, TbRA9, TbRA10, TbRA13, TbRA17, TbRA19, TbRA29, TbRA32, TbRA36 and the overlapping clones TbRA35 and TbRA12 (SEQ ID Nos. 64, 78, 82, 83, 65, 68, 76, 72, 76, 79, 81, 80, 67, respectively). The clone TbRa24 is overlapping with clone TbRa29.

B. USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

The genomic DNA library described above, and an additional H37Rv library, were screened using pools of sera obtained from patients with active tuberculosis. To prepare the H37Rv library, *M. tuberculosis* strain H37Rv genomic DNA was isolated, subjected to partial Sau3A digestion and used to construct an expression library using the Lambda Zap expression system (Stratagene, La Jolla, Ca). Three different pools of sera, each containing sera obtained from three individuals with active pulmonary or pleural disease, were used in the expression screening. The pools were designated TbL, TbM and TbH, referring to relative reactivity with H37Ra lysate (*i.e.*, TbL = low reactivity, TbM = medium reactivity and TbH = high reactivity) in both ELISA and immunoblot format. A fourth pool of sera from seven patients with active pulmonary tuberculosis was also employed. All of the sera lacked increased reactivity with the recombinant 38 kD *M. tuberculosis* H37Ra phosphate-binding protein.

All pools were pre-adsorbed with *E. coli* lysate and used to screen the H37Ra and H37Rv expression libraries, as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 31 represented sequences that had not been previously identified in human *M. tuberculosis*. Representative sequences of the DNA molecules identified are provided in SEQ ID NOS.: 26-51 and 100. Of these, TbH-8 and TbH-8-2 (SEQ. ID NO. 100) are non-contiguous DNA sequences from the same clone, and TbH-4 (SEQ. ID NO. 43) and TbH-4-FWD (SEQ. ID NO. 44) are non-contiguous sequences from the same clone. Amino acid sequences for the antigens hereinafter identified as Tb38-1, TbH-4, TbH-8, TbH-9, and TbH-12 are shown in SEQ ID NOS.: 89-93. Comparison of these sequences with known sequences in the gene bank using the databases identified above revealed no significant homologies to TbH-4, TbH-8, TbH-9 and TbM-3, although weak homologies were

found to TbH-9. TbH-12 was found to be homologous to a 34 kD antigenic protein previously identified in *M. paratuberculosis* (Acc. No. S28515). Tb38-1 was found to be located 34 base pairs upstream of the open reading frame for the antigen ESAT-6 previously identified in *M. bovis* (Acc. No. U34848) and in *M. tuberculosis* (Sorensen et al., *Infec. Immun. 63*:1710-1717, 1995).

Probes derived from Tb38-1 and TbH-9, both isolated from an H37Ra library, were used to identify clones in an H37Rv library. Tb38-1 hybridized to Tb38-1F2, Tb38-1F3, Tb38-1F5 and Tb38-1F6 (SEQ. ID NOS. 107, 108, 111, 113, and 114). (SEQ ID NOS. 107 and 108 are non-contiguous sequences from clone Tb38-1F2.) Two open reading frames were deduced in Tb38-IF2; one corresponds to Tb37FL (SEQ. ID. NO. 109), the second, a partial sequence, may be the homologue of Tb38-1 and is called Tb38-IN (SEQ. ID NO. 110). The deduced amino acid sequence of Tb38-1F3 is presented in SEQ. ID. NO. 112. A TbH-9 probe identified three clones in the H37Rv library: TbH-9-FL (SEQ. ID NO. 101), which may be the homologue of TbH-9 (R37Ra), TbH-9-1 (SEQ. ID NO. 103), and TbH-9-4 (SEQ. ID NO. 105), all of which are highly related sequences to TbH-9. The deduced amino acid sequences for these three clones are presented in SEQ ID NOS. 102, 104 and 106.

EXAMPLE 4

PURIFICATION AND CHARACTERIZATION OF A POLYPEPTIDE FROM TUBERCULIN PURIFIED PROTEIN DERIVATIVE

An *M. tuberculosis* polypeptide was isolated from tuberculin purified protein derivative (PPD) as follows.

PPD was prepared as published with some modification (Seibert, F. et al., Tuberculin purified protein derivative. Preparation and analyses of a large quantity for standard. The American Review of Tuberculosis 44:9-25, 1941). *M. tuberculosis* Rv strain was grown for 6 weeks in synthetic medium in roller bottles at 37 °C. Bottles containing the bacterial growth were then heated to 100°C in water vapor

for 3 hours. Cultures were sterile filtered using a 0.22 μ filter and the liquid phase was concentrated 20 times using a 3 kD cut-off membrane. Proteins were precipitated once with 50% ammonium sulfate solution and eight times with 25% ammonium sulfate solution. The resulting proteins (PPD) were fractionated by reverse phase liquid chromatography (RP-HPLC) using a C18 column (7.8 x 300 mM; Waters, Milford, MA) in a Biocad HPLC system (Perseptive Biosystems, Framingham, MA). Fractions were eluted from the column with a linear gradient from 0-100% buffer (0.1% TFA in acetonitrile). The flow rate was 10 ml/minute and eluent was monitored at 214 nm and 280 nm.

Six fractions were collected, dried, suspended in PBS and tested individually in *M. tuberculosis*-infected guinea pigs for induction of delayed type hypersensitivity (DTH) reaction. One fraction was found to induce a strong DTH reaction and was subsequently fractionated furtherby RP-HPLC on a microbore Vydac C18 column (Cat. No. 218TP5115) in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted with a linear gradient from 5-100% buffer (0.05% TFA in acetonitrile) with a flow rate of 80 μl/minute. Eluent was monitored at 215 nm. Eight fractions were collected and tested for induction of DTH in *M. tuberculosis*-infected guinea pigs. One fraction was found to induce strong DTH of about 16 mm induration. The other fractions did not induce detectable DTH. The positive fraction was submitted to SDS-PAGE gel electrophoresis and found to contain a single protein band of approximately 12 kD molecular weight.

This polypeptide, herein after referred to as DPPD, was sequenced from the amino terminal using a Perkin Elmer/Applied Biosystems Division Procise 492 protein sequencer as described above and found to have the N-terminal sequence shown in SEQ ID No.: 124. Comparison of this sequence with known sequences in the gene bank as described above revealed no known homologies. Four cyanogen bromide fragments of DPPD were isolated and found to have the sequences shown in SEQ ID Nos.: 125-128.

EXAMPLE 5

SYNTHESIS OF SYNTHETIC POLYPEPTIDES

Polypeptides may be synthesized on a Millipore 9050 peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray mass spectrometry and by amino acid analysis.

This procedure was used to synthesize a TbM-1 peptide that contains one and a half repeats of a TbM-1 sequence. The TbM-1 peptide has the sequence GCGDRSGGNLDQIRLRRDRSGGNL (SEQ ID No. 63).

EXAMPLE 6

USE OF REPRESENTATIVE ANTIGENS FOR SERODIAGNOSIS OF TUBERCULOSIS

This Example illustrates the diagnostic properties of several representative antigens. Figures 1 and 2 present the reactivity of representative antigens with sera from *M. tuberculosis*-infected and uninfected individuals, as compared to the reactivity of bacterial lysate and the 38 kD antigen.

Assays were performed in 96-well plates were coated with 200 ng antigen diluted to 50 µL in carbonate coating buffer, pH 9.6. The wells were coated

overnight at 4°C (or 2 hours at 37°C). The plate contents were then removed and the wells were blocked for 2 hours with 200 µL of PBS/1% BSA. After the blocking step, the wells were washed five times with PBS/0.1% Tween 20™. 50 µL sera, diluted 1:100 in PBS/0.1% Tween 20™/0.1% BSA, was then added to each well and incubated for 30 minutes at room temperature. The plates were then washed again five times with PBS/0.1% Tween 20™.

The enzyme conjugate (horseradish peroxidase - Protein A, Zymed, San Francisco, CA) was then diluted 1:10,000 in PBS/0.1% Tween 20™/0.1% BSA, and 50 µL of the diluted conjugate was added to each well and incubated for 30 minutes at room temperature. Following incubation, the wells were washed five times with PBS/0.1% Tween 20™. 100 µL of tetramethylbenzidine peroxidase (TMB) substrate (Kirkegaard and Perry Laboratories, Gaithersburg, MD) was added, undiluted, and incubated for about 15 minutes. The reaction was stopped with the addition of 100 µL of 1 N H_2SO_4 to each well, and the plates were read at 450 nm.

Figure 2 shows the ELISA reactivity of two recombinant antigens isolated using method A in Example 3 (TbRa3 and TbRa9) with sera from *M. tuberculosis* positive and negative patients. The reactivity of these antigens is compared to that of bacterial lysate isolated from *M. tuberculosis* strain H37Ra (Difco, Detroit, MI). In both cases, the recombinant antigens differentiated positive from negative sera. Based on cut-off values obtained from receiver-operator curves, TbRa3 detected 56 out of 87 positive sera, and TbRa9 detected 111 out of 165 positive sera.

Figure 3 illustrates the ELISA reactivity of representative antigens isolated using method B of Example 3. The reactivity of the recombinant antigens TbH4, TbH12, Tb38-1 and the peptide TbM-1 (as described in Example 4) is compared to that of the 38 kD antigen described by Andersen and Hansen, *Infect. Immun.* *57*:2481-2488, 1989. Again, all of the polypeptides tested differentiated positive from negative sera. Based on cut-off values obtained from receiver-operator curves, TbH4 detected 67 out of 126 positive sera, TbH12 detected 50 out of 125 positive sera, 38-1 detected 61 out of 101 positive sera and the TbM-1 peptide detected 25 out of 30 positive sera.

The reactivity of four antigens (TbRa3, TbRa9, TbH4 and TbH12) with sera from a group of *M. tuberculosis* infected patients with differing reactivity in the acid fast stain of sputum (Smithwick and David, *Tubercle 52*:226, 1971) was also examined, and compared to the reactivity of *M. tuberculosis* lysate and the 38 kD antigen. The results are presented in Table 2, below:

TABLE 2

REACTIVITY OF ANTIGENS WITH SERA FROM *M. TUBERCULOSIS* PATIENTS

Patient	Acid Fast Sputum	ELISA Values					
		Lysate	38kD	TbRa9	TbH12	TbH4	TbRa3
Tb01B93I-2	++++	1.853	0.634	0.998	1.022	1.030	1.314
Tb01B93I-19	++++	2.657	2.322	0.608	0.837	1.857	2.335
Tb01B93I-8	+++	2.703	0.527	0.492	0.281	0.501	2.002
Tb01B93I-10	+++	1.665	1.301	0.685	0.216	0.448	0.458
Tb01B93I-11	+++	2.817	0.697	0.509	0.301	0.173	2.608
Tb01B93I-15	+++	1.28	0.283	0.808	0.218	1.537	0.811
Tb01B93I-16	+++	2.908	>3	0.899	0.441	0.593	1.080
Tb01B93I-25	+++	0.395	0.131	0.335	0.211	0.107	0.948
Tb01B93I-87	+++	2.653	2.432	2.282	0.977	1.221	0.857
Tb01B93I-89	+++	1.912	2.370	2.436	0.876	0.520	0.952
Tb01B94I-108	+++	1.639	0.341	0.797	0.368	0.654	0.798
Tb01B94I-201	+++	1.721	0.419	0.661	0.137	0.064	0.692
Tb01B93I-88	++	1.939	1.269	2.519	1.381	0.214	0.530
Tb01B93I-92	++	2.355	2.329	2.78	0.685	0.997	2.527
Tb01B94I-109	++	0.993	0.620	0.574	0.441	0.5	2.558

Patient	Acid Fast Sputum	ELISA Values					
		Lysate	38kD	TbRa9	TbH12	TbH4	TbRa3
Tb01B94I-210	++	2.777	>3	0.393	0.367	1.004	1.315
Tb01B94I-224	++	2.913	0.476	0.251	1.297	1.990	0.256
Tb01B93I-9	+	2.649	0.278	0.210	0.140	0.181	1.586
Tb01B93I-14	+	>3	1.538	0.282	0.291	0.549	2.880
Tb01B93I-21	+	2.645	0.739	2.499	0.783	0.536	1.770
Tb01B93I-22	+	0.714	0.451	2.082	0.285	0.269	1.159
Tb01B93I-31	+	0.956	0.490	1.019	0.812	0.176	1.293
Tb01B93I-32	–	2.261	0.786	0.668	0.273	0.535	0.405
Tb01B93I-52	–	0.658	0.114	0.434	0.330	0.273	1.140
Tb01B93I-99	–	2.118	0.584	1.62	0.119	0.977	0.729
Tb01B94I-130	–	1.349	0.224	0.86	0.282	0.383	2.146
Tb01B94I-131	–	0.685	0.324	1.173	0.059	0.118	1.431
AT4-0070	Normal	0.072	0.043	0.092	0.071	0.040	0.039
AT4-0105	Normal	0.397	0.121	0.118	0.103	0.078	0.390
3/15/94-1	Normal	0.227	0.064	0.098	0.026	0.001	0.228
4/15/93-2	Normal	0.114	0.240	0.071	0.034	0.041	0.264
5/26/94-4	Normal	0.089	0.259	0.096	0.046	0.008	0.053
5/26/94-3	Normal	0.139	0.093	0.085	0.019	0.067	0.01

Based on cut-off values obtained from receiver-operator curves, TbRa3 detected 23 out of 27 positive sera, TbRa9 detected 22 out of 27, TbH4 detected 18 out of 27 and TbH12 detected 15 out of 27. If used in combination, these four antigens would have a theoretical sensitivity of 27 out of 27, indicating that these antigens should complement each other in the serological detection of *M. tuberculosis* infection.

In addition, several of the recombinant antigens detected positive sera that were not detected using the 38 kD antigen, indicating that these antigens may be complementary to the 38 kD antigen.

The reactivity of the recombinant antigen TbRa11 with sera from *M. tuberculosis* patients shown to be negative for the 38 kD antigen, as well as with sera from PPD positive and normal donors, was determined by ELISA as described above. The results are shown in Figure 4 which indicates that TbRa11, while being negative with sera from PPD positive and normal donors, detected sera that were negative with the 38 kD antigen. Of the thirteen 38 kD negative sera tested, nine were positive with TbRa11, indicating that this antigen may be reacting with a sub-group of 38 kD antigen negative sera. In contrast, in a group of 38 kD positive sera where TbRa11 was reactive, the mean OD 450 for TbRa11 was lower than that for the 38 kD antigen. The data indicate an inverse relationship between the presence of TbRa11 activity and 38 kD positivity.

The antigen TbRa2A was tested in an indirect ELISA using initially 50 µl of serum at 1:100 dilution for 30 minutes at room temperature followed by washing in PBS Tween and incubating for 30 minutes with biotinylated Protein A (Zymed, San Francisco, CA) at a 1:10,000 dilution. Following washing, 50 µl of streptavidin-horseradish peroxidase (Zymed) at 1:10,000 dilution was added and the mixture incubated for 30 minutes. After washing, the assay was developed with TMB substrate as described above. The reactivity of TbRa2A with sera from *M. tuberculosis* patients and normal donors in shown in Table 3. The mean value for reactivity of TbRa2A with sera from *M. tuberculosis* patients was 0.444 with a standard deviation of 0.309. The mean for reactivity with sera from normal donors was 0.109 with a standard deviation of 0.029. Testing of 38 kD negative sera (Figure 5) also indicated that the TbRa2A antigen was capable of detecting sera in this category.

TABLE 3

REACTIVITY OF TBRA2A WITH SERA FROM *M. TUBERCULOSIS* PATIENTS AND FROM NORMAL DONORS

Serum ID	Status	OD 450
Tb85	TB	0.680
Tb86	TB	0.450
Tb87	TB	0.263
Tb88	TB	0.275
Tb89	TB	0.403
Tb91	TB	0.393
Tb92	TB	0.401
Tb93	TB	0.232
Tb94	TB	0.333
Tb95	TB	0.435
Tb96	TB	0.284
Tb97	TB	0.320
Tb99	TB	0.328
Tb100	TB	0.817
Tb101	TB	0.607
Tb102	TB	0.191
Tb103	TB	0.228
Tb107	TB	0.324
Tb109	TB	1.572
Tb112	TB	0.338
DL4-0176	Normal	0.036
AT4-0043	Normal	0.126
AT4-0044	Normal	0.130
AT4-0052	Normal	0.135
AT4-0053	Normal	0.133
AT4-0062	Normal	0.128
AT4-0070	Normal	0.088
AT4-0091	Normal	0.108
AT4-0100	Normal	0.106
AT4-0105	Normal	0.108
AT4-0109	Normal	0.105

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The reactivity of the recombinant antigen (g) (SEQ ID No. 60) with sera from *M. tuberculosis* patients and normal donors was determined by ELISA as described above. Figure 6 shows the results of the titration of antigen (g) with four

M. tuberculosis positive sera that were all reactive with the 38 kD antigen and with four donor sera. All four positive sera were reactive with antigen (g).

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANTS: Corixa Corporation

(ii) TITLE OF INVENTION: COMPOUNDS AND METHODS FOR DIAGNOSIS OF TUBERCULOSIS

(iii) NUMBER OF SEQUENCES: 132

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(C) CITY: Seattle
(D) STATE: Washington
(E) COUNTRY: USA
(F) ZIP: 98104-7092

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 27-AUG-1996
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Maki, David J.
(B) REGISTRATION NUMBER: 31,392
(C) REFERENCE/DOCKET NUMBER: 210121.417PC

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (206) 622-4900
(B) TELEFAX: (206) 682-6031

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 766 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGAGGCACCG GTAGTTTGAA CCAAACGCAC AATCGACGGG CAAACGAACG GAAGAACACA 60

ACCATGAAGA TGGTGAAATC GATCGCCGCA GGTCTGACCG CCGCGGCTGC AATCGGCGCC 120

GCTGCGGCCG GTGTGACTTC GATCATGGCT GGCGGCCCGG TCGTATACCA GATGCAGCCG 180

GTCGTCTTCG GCGCGCCACT GCCGTTGGAC CCGGCATCCG CCCCTGACGT CCCGACCGCC 240

GCCCAGTTGA CCAGCCTGCT CAACAGCCTC GCCGATCCCA ACGTGTCGTT TGCGAACAAG 300

GGCAGTCTGG TCGAGGGCGG CATCGGGGGC ACCGAGGCGC GCATCGCCGA CCACAAGCTG 360

AAGAAGGCCG CCGAGCACGG GGATCTGCCG CTGTCGTTCA GCGTGACGAA CATCCAGCCG 420

GCGGCCGCCG GTTCGGCCAC CGCCGACGTT TCCGTCTCGG GTCCGAAGCT CTCGTCGCCG 480

GTCACGCAGA ACGTCACGTT CGTGAATCAA GGCGGCTGGA TGCTGTCACG CGCATCGGCG 540

ATGGAGTTGC TGCAGGCCGC AGGGNAACTG ATTGGCGGGC CGGNTTCAGC CCGCTGTTCA 600

GCTACGCCGC CCGCCTGGTG ACGCGTCCAT GTCGAACACT CGCGCGTGTA GCACGGTGCG 660

GTNTGCGCAG GGNCGCACGC ACCGCCCGGT GCAAGCCGTC CTCGAGATAG GTGGTGNCTC 720

GNCACCAGNG ANCACCCCCN NNTCGNCNNT TCTCGNTGNT GNATGA 766

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 752 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGCATCACC ATCACCATCA CGATGAAGTC ACGGTAGAGA CGACCTCCGT CTTCCGCGCA 60

GACTTCCTCA GCGAGCTGGA CGCTCCTGCG CAAGCGGGTA CGGAGAGCGC GGTCTCCGGG 120

GTGGAAGGGC TCCCGCCGGG CTCGGCGTTG CTGGTAGTCA AACGAGGCCC CAACGCCGGG 180

TCCCGGTTCC TACTCGACCA AGCCATCACG TCGGCTGGTC GGCATCCCGA CAGCGACATA 240

TTTCTCGACG ACGTGACCGT GAGCCGTCGC CATGCTGAAT TCCGGTTGGA AAACAACGAA 300

TTCAATGTCG TCGATGTCGG GAGTCTCAAC GGCACCTACG TCAACCGCGA GCCCGTGGAT 360

TCGGCGGTGC TGGCGAACGG CGACGAGGTC CAGATCGGCA AGCTCCGGTT GGTGTTCTTG 420

ACCGGACCCA AGCAAGGCGA GGATGACGGG AGTACCGGGG GCCCGTGAGC GCACCCGATA 480

GCCCCGCGCT GGCCGGGATG TCGATCGGGG CGGTCCTCCG ACCTGCTACG ACCGGATTTT 540

CCCTGATGTC CACCATCTCC AAGATTCGAT TCTTGGGAGG CTTGAGGGTC NGGGTGACCC 600

CCCCGCGGGC CTCATTCNGG GGTNTCGGCN GGTTTCACCC CNTACCNACT GCCNCCCGGN 660

TTGCNAATTC NTTCTTCNCT GCCCNNAAAG GGACCNTTAN CTTGCCGCTN GAAANGGTNA 720

TCCNGGGCCC NTCCTNGAAN CCCCNTCCCC CT 752

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 813 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATATGCATC ACCATCACCA TCACACTTCT AACCGCCCAG CGCGTCGGGG GCGTCGAGCA 60

CCACGCGACA CCGGGCCCGA TCGATCTGCT AGCTTGAGTC TGGTCAGGCA TCGTCGTCAG 120

CAGCGCGATG CCCTATGTTT GTCGTCGACT CAGATATCGC GGCAATCCAA TCTCCCGCCT 180

GCGGCCGGCG GTGCTGCAAA CTACTCCCGG AGGAATTTCG ACGTGCGCAT CAAGATCTTC 240

ATGCTGGTCA CGGCTGTCGT TTTGCTCTGT TGTTCGGGTG TGGCCACGGC CGCGCCCAAG 300

ACCTACTGCG AGGAGTTGAA AGGCACCGAT ACCGGCCAGG CGTGCCAGAT TCAAATGTCC 360

GACCCGGCCT ACAACATCAA CATCAGCCTG CCCAGTTACT ACCCCGACCA GAAGTCGCTG 420

GAAAATTACA TCGCCCAGAC GCGCGACAAG TTCCTCAGCG CGGCCACATC GTCCACTCCA 480

CGCGAAGCCC CCTACGAATT GAATATCACC TCGGCCACAT ACCAGTCCGC GATACCGCCG 540

CGTGGTACGC AGGCCGTGGT GCTCAMGGTC TACCACAACG CCGGCGGCAC GCACCCAACG 600

ACCACGTACA AGGCCTTCGA TTGGGACCAG GCCTATCGCA AGCCAATCAC CTATGACACG 660

CTGTGGCAGG CTGACACCGA TCCGCTGCCA GTCGTCTTCC CCATTGTTGC AAGGTGAACT 720

GAGCAACGCA GACCGGGACA ACWGGTATCG ATAGCCGCCN AATGCCGGCT TGGAACCCNG 780

TGAAATTATC ACAACTTCGC AGTCACNAAA NAA 813

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 447 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGTATGAAC ACGGCCGCGT CCGATAACTT CCAGCTGTCC CAGGGTGGGC AGGGATTCGC 60

CATTCCGATC GGGCAGGCGA TGGCGATCGC GGGCCAGATC CGATCGGGTG GGGGGTCACC 120

CACCGTTCAT ATCGGGCCTA CCGCCTTCCT CGGCTTGGGT GTTGTCGACA ACAACGGCAA 180

CGGCGCACGA GTCCAACGCG TGGTCGGGAG CGCTCCGGCG GCAAGTCTCG GCATCTCCAC 240

CGGCGACGTG ATCACCGCGG TCGACGGCGC TCCGATCAAC TCGGCCACCG CGATGGCGGA 300

CGCGCTTAAC GGGCATCATC CCGGTGACGT CATCTCGGTG AACTGGCAAA CCAAGTCGGG 360

CGGCACGCGT ACAGGGAACG TGACATTGGC CGAGGGACCC CCGGCCTGAT TTCGTCGYGG 420

ATACCACCCG CCGGCCGGCC AATTGGA 447

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 604 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTCCCACTGC GGTCGCCGAG TATGTCGCCC AGCAAATGTC TGGCAGCCGC CCAACGGAAT 60

CCGGTGATCC GACGTCGCAG GTTGTCGAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT 120

AGCCCGGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCGGGCAAT TTGGCGGGGC 180

CCGGCGACGG NGAGCGCCGG AATGGCGCGA GTGAGGAGGT GGNCAGTCAT GCCCAGNGTG 240

ATCCAATCAA CCTGNATTCG GNCTGNGGGN CCATTTGACA ATCGAGGTAG TGAGCGCAAA 300

TGAATGATGG AAAACGGGNG GNGACGTCCG NTGTTCTGGT GGTGNTAGGT GNCTGNCTGG 360

NGTNGNGGNT ATCAGGATGT TCTTCGNCGA AANCTGATGN CGAGGAACAG GGTGTNCCCG 420

NNANNCCNAN GGNGTCCNAN CCCNNNNTCC TCGNCGANAT CANANAGNCG NTTGATGNGA 480

NAAAAGGGTG GANCAGNNNN AANTNGNGGN CCNAANAANC NNNANNGNNG NNAGNTNGNT 540

NNNTNTTNNC ANNNNNNNTG NNGNNGNNCN NNNCAANCNN NTNNNNGNAA NNGGNTTNTT 600

NAAT 604

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 633 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TTGCANGTCG AACCACCTCA CTAAAGGGAA CAAAAGCTNG AGCTCCACCG CGGTGGCGGC 60

CGCTCTAGAA CTAGTGKATM YYYCKGGCTG CAGSAATYCG GYACGAGCAT TAGGACAGTC 120

TAACGGTCCT GTTACGGTGA TCGAATGACC GACGACATCC TGCTGATCGA CACCGACGAA 180

CGGGTGCGAA CCCTCACCCT CAACCGGCCG CAGTCCCGYA ACGCGCTCTC GGCGGCGCTA 240

CGGGATCGGT TTTTCGCGGY GTTGGYCGAC GCCGAGGYCG ACGACGACAT CGACGTCGTC 300

ATCCTCACCG GYGCCGATCC GGTGTTCTGC GCCGGACTGG ACCTCAAGGT AGCTGGCCGG 360

GCAGACCGCG CTGCCGGACA TCTCACCGCG GTGGGCGGCC ATGACCAAGC CGGTGATCGG 420

CGCGATCAAC GGCGCCGCGG TCACCGGCGG GCTCGAACTG GCGCTGTACT GCGACATCCT 480

GATCGCCTCC GAGCACGCCC GCTTCGNCGA CACCCACGCC CGGGTGGGGC TGCTGCCCAC 540

CTGGGGACTC AGTGTGTGCT TGCCGCAAAA GGTCGGCATC GGNCTGGGCC GGTGGATGAG 600

CCTGACCGGC GACTACCTGT CCGTGACCGA CGC 633

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1362 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CGACGACGAC GGCGCCGGAG AGCGGGCGCG AACGGCGATC GACGCGGCCC TGGCCAGAGT 60

CGGCACCACC CAGGAGGGAG TCGAATCATG AAATTTGTCA ACCATATTGA GCCCGTCGCG 120

CCCCGCCGAG CCGGCGGCGC GGTCGCCGAG GTCTATGCCG AGGCCCGCCG CGAGTTCGGC 180

CGGCTGCCCG AGCCGCTCGC CATGCTGTCC CCGGACGAGG GACTGCTCAC CGCCGGCTGG 240

GCGACGTTGC GCGAGACACT GCTGGTGGGC CAGGTGCCGC GTGGCCGCAA GGAAGCCGTC 300

GCCGCCGCCG TCGCGGCCAG CCTGCGCTGC CCCTGGTGCG TCGACGCACA CACCACCATG 360

CTGTACGCGG CAGGCCAAAC CGACACCGCC GCGGCGATCT TGGCCGGCAC AGCACCTGCC 420

GCCGGTGACC CGAACGCGCC GTATGTGGCG TGGGCGGCAG GAACCGGGAC ACCGGCGGGA 480

CCGCCGGCAC CGTTCGGCCC GGATGTCGCC GCCGAATACC TGGGCACCGC GGTGCAATTC 540

CACTTCATCG CACGCCTGGT CCTGGTGCTG CTGGACGAAA CCTTCCTGCC GGGGGGCCCG 600

CGCGCCCAAC AGCTCATGCG CCGCGCCGGT GGACTGGTGT TCGCCCGCAA GGTGCGCGCG 660

GAGCATCGGC CGGGCCGCTC CACCCGCCGG CTCGAGCCGC GAACGCTGCC CGACGATCTG 720

GCATGGGCAA CACCGTCCGA GCCCATAGCA ACCGCGTTCG CCGCGCTCAG CCACCACCTG 780

GACACCGCGC CGCACCTGCC GCCACCGACT CGTCAGGTGG TCAGGCGGGT CGTGGGGTCG 840

TGGCACGGCG AGCCAATGCC GATGAGCAGT CGCTGGACGA ACGAGCACAC CGCCGAGCTG 900

CCCGCCGACC TGCACGCGCC CACCCGTCTT GCCCTGCTGA CCGGCCTGGC CCCGCATCAG 960

GTGACCGACG ACGACGTCGC CGCGGCCCGA TCCCTGCTCG ACACCGATGC GGCGCTGGTT 1020

GGCGCCCTGG CCTGGGCCGC CTTCACCGCC GCGCGGCGCA TCGGCACCTG GATCGGCGCC 1080

GCCGCCGAGG GCCAGGTGTC GCGGCAAAAC CCGACTGGGT GAGTGTGCGC GCCCTGTCGG 1140

TAGGGTGTCA TCGCTGGCCC GAGGGATCTC GCGGCGGCGA ACGGAGGTGG CGACACAGGT 1200

GGAAGCTGCG CCCACTGGCT TGCGCCCCAA CGCCGTCGTG GGCGTTCGGT TGGCCGCACT 1260

GGCCGATCAG GTCGGCGCCG GCCCTTGGCC GAAGGTCCAG CTCAACGTGC CGTCACCGAA 1320

GGACCGGACG GTCACCGGGG GTCACCCTGC GCGCCCAAGG AA 1362

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1458 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCGACGACCC CGATATGCCG GGCACCGTAG CGAAAGCCGT CGCCGACGCA CTCGGGCGCG 60

GTATCGCTCC CGTTGAGGAC ATTCAGGACT GCGTGGAGGC CCGGCTGGGG GAAGCCGGTC 120

TGGATGACGT GGCCCGTGTT TACATCATCT ACCGGCAGCG GCGCGCCGAG CTGCGGACGG 180

CTAAGGCCTT GCTCGGCGTG CGGGACGAGT TAAAGCTGAG CTTGGCGGCC GTGACGGTAC 240

TGCGCGAGCG CTATCTGCTG CACGACGAGC AGGGCCGGCC GGCCGAGTCG ACCGGCGAGC 300

TGATGGACCG ATCGGCGCGC TGTGTCGCGG CGGCCGAGGA CCAGTATGAG CCGGGCTCGT 360

CGAGGCGGTG GGCCGAGCGG TTCGCCACGC TATTACGCAA CCTGGAATTC CTGCCGAATT 420

CGCCCACGTT GATGAACTCT GGCACCGACC TGGGACTGCT CGCCGGCTGT TTTGTTCTGC 480

CGATTGAGGA TTCGCTGCAA TCGATCTTTG CGACGCTGGG ACAGGCCGCC GAGCTGCAGC 540

GGGCTGGAGG CGGCACCGGA TATGCGTTCA GCCACCTGCG ACCCGCCGGG GATCGGGTGG 600

CCTCCACGGG CGGCACGGCC AGCGGACCGG TGTCGTTTCT ACGGCTGTAT GACAGTGCCG 660

CGGGTGTGGT CTCCATGGGC GGTCGCCGGC GTGGCGCCTG TATGGCTGTG CTTGATGTGT 720

CGCACCCGGA TATCTGTGAT TTCGTCACCG CCAAGGCCGA ATCCCCCAGC GAGCTCCCGC 780

ATTTCAACCT ATCGGTTGGT GTGACCGACG CGTTCCTGCG GGCCGTCGAA CGCAACGGCC 840

TACACCGGCT GGTCAATCCG CGAACCGGCA AGATCGTCGC GCGGATGCCC GCCGCCGAGC 900

TGTTCGACGC CATCTGCAAA GCCGCGCACG CCGGTGGCGA TCCCGGGCTG GTGTTTCTCG 960

ACACGATCAA TAGGGCAAAC CCGGTGCCGG GGAGAGGCCG CATCGAGGCG ACCAACCCGT 1020

GCGGGGAGGT CCCACTGCTG CCTTACGAGT CATGTAATCT CGGCTCGATC AACCTCGCCC 1080

GGATGCTCGC CGACGGTCGC GTCGACTGGG ACCGGCTCGA GGAGGTCGCC GGTGTGGCGG 1140

TGCGGTTCCT TGATGACGTC ATCGATGTCA GCCGCTACCC CTTCCCCGAA CTGGGTGAGG 1200

CGGCCCGCGC CACCCGCAAG ATCGGGCTGG GAGTCATGGG TTTGGCGGAA CTGCTTGCCG 1260

CACTGGGTAT TCCGTACGAC AGTGAAGAAG CCGTGCGGTT AGCCACCCGG CTCATGCGTC 1320

GCATACAGCA GGCGGCGCAC ACGGCATCGC GGAGGCTGGC CGAAGAGCGG GGCGCATTCC 1380

CGGCGTTCAC CGATAGCCGG TTCGCGCGGT CGGGCCCGAG GCGCAACGCA CAGGTCACCT 1440

CCGTCGCTCC GACGGGCA 1458

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 862 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACGGTGTAAT CGTGCTGGAT CTGGAACCGC GTGGCCCGCT ACCTACCGAG ATCTACTGGC 60

GGCGCAGGGG GCTGGCCCTG GGCATCGCGG TCGTCGTAGT CGGGATCGCG GTGGCCATCG 120

TCATCGCCTT CGTCGACAGC AGCGCCGGTG CCAAACCGGT CAGCGCCGAC AAGCCGGCCT 180

CCGCCCAGAG CCATCCGGGC TCGCCGGCAC CCCAAGCACC CCAGCCGGCC GGGCAAACCG 240

AAGGTAACGC CGCCGCGGCC CCGCCGCAGG GCCAAAACCC CGAGACACCC ACGCCCACCG 300

CCGCGGTGCA GCCGCCGCCG GTGCTCAAGG AAGGGGACGA TTGCCCCGAT TCGACGCTGG 360

CCGTCAAAGG TTTGACCAAC GCGCCGCAGT ACTACGTCGG CGACCAGCCG AAGTTCACCA 420

TGGTGGTCAC CAACATCGGC CTGGTGTCCT GTAAACGCGA CGTTGGGGCC GCGGTGTTGG 480

CCGCCTACGT TTACTCGCTG GACAACAAGC GGTTGTGGTC CAACCTGGAC TGCGCGCCCT 540

CGAATGAGAC GCTGGTCAAG ACGTTTTCCC CCGGTGAGCA GGTAACGACC GCGGTGACCT 600

GGACCGGGAT GGGATCGGCG CCGCGCTGCC CATTGCCGCG GCCGGCGATC GGGCCGGGCA 660

CCTACAATCT CGTGGTACAA CTGGGCAATC TGCGCTCGCT GCCGGTTCCG TTCATCCTGA 720

ATCAGCCGCC GCCGCCGCCC GGGCCGGTAC CCGCTCCGGG TCCAGCGCAG GCGCCTCCGC 780

CGGAGTCTCC CGCGCAAGGC GGATAATTAT TGATCGCTGA TGGTCGATTC CGCCAGCTGT 840

GACAACCCCT CGCCTCGTGC CG 862

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 622 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC CAATGACAAA 60

GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC GAACGCTGGA 120

GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG CGCGGACGCG 180

TTGGTTGCCG CCGTGCGGTC CAAAGCGCCG GGCGCCACGG TGGCGCTAAC CTTTCAGGAT 240

CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA GTGATGAAGG 300

TCGCCGCGCA GTGTTCAAAG CTCGGATATA CGGTGGCACC CATGGAACAG CGTGCGGAGT 360

TGGTGGTTGG CCGGGCACTT GTCGTCGTCG TTGACGATCG CACGGCGCAC GGCGATGAAG 420

ACCACAGCGG GCCGCTTGTC ACCGAGCTGC TCACCGAGGC CGGGTTTGTT GTCGACGGCG 480

TGGTGGCGGT GTCGGCCGAC GAGGTCGAGA TCCGAAATGC GCTGAACACA GCGGTGATCG 540

GCGGGGTGGA CCTGGTGGTG TCGGTCGGCG GGACCGGNGT GACGNCTCGC GATGTCACCC 600

CGGAAGCCAC CCGNGACATT CT 622

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1200 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGCGCAGCGG TAAGCCTGTT GGCCGCCGGC ACACTGGTGT TGACAGCATG CGGCGGTGGC 60

ACCAACAGCT CGTCGTCAGG CGCAGGCGGA ACGTCTGGGT CGGTGCACTG CGGCGGCAAG 120

AAGGAGCTCC ACTCCAGCGG CTCGACCGCA CAAGAAAATG CCATGGAGCA GTTCGTCTAT 180

GCCTACGTGC GATCGTGCCC GGGCTACACG TTGGACTACA ACGCCAACGG GTCCGGTGCC 240

GGGGTGACCC AGTTTCTCAA CAACGAAACC GATTTCGCCG GCTCGGATGT CCCGTTGAAT 300

CCGTCGACCG GTCAACCTGA CCGGTCGGCG GAGCGGTGCG GTTCCCCGGC ATGGGACCTG 360

CCGACGGTGT TCGGCCCGAT CGCGATCACC TACAATATCA AGGGCGTGAG CACGCTGAAT 420

CTTGACGGAC CCACTACCGC CAAGATTTTC AACGGCACCA TCACCGTGTG GAATGATCCA 480

CAGATCCAAG CCCTCAACTC CGGCACCGAC CTGCCGCCAA CACCGATTAG CGTTATCTTC 540

CGCAGCGACA AGTCCGGTAC GTCGGACAAC TTCCAGAAAT ACCTCGACGG TGTATCCAAC 600

GGGGCGTGGG GCAAAGGCGC CAGCGAAACG TTCAGCGGGG GCGTCGGCGT CGGCGCCAGC 660

GGGAACAACG GAACGTCGGC CCTACTGCAG ACGACCGACG GGTCGATCAC CTACAACGAG 720

TGGTCGTTTG CGGTGGGTAA GCAGTTGAAC ATGGCCCAGA TCATCACGTC GGCGGGTCCG 780

GATCCAGTGG CGATCACCAC CGAGTCGGTC GGTAAGACAA TCGCCGGGGC CAAGATCATG 840

GGACAAGGCA ACGACCTGGT ATTGGACACG TCGTCGTTCT ACAGACCCAC CCAGCCTGGC 900

TCTTACCCGA TCGTGCTGGC GACCTATGAG ATCGTCTGCT CGAAATACCC GGATGCGACG 960

ACCGGTACTG CGGTAAGGGC GTTTATGCAA GCCGCGATTG GTCCAGGCCA AGAAGGCCTG 1020

GACCAATACG GCTCCATTCC GTTGCCCAAA TCGTTCCAAG CAAAATTGGC GGCCGCGGTG 1080

AATGCTATTT CTTGACCTAG TGAAGGGAAT TCGACGGTGA GCGATGCCGT TCCGCAGGTA 1140

GGGTCGCAAT TTGGGCCGTA TCAGCTATTG CGGCTGCTGG GCCGAGGCGG GATGGGCGAG 1200

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1155 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAAGCAGCT GCAGGTCGTG CTGTTCGACG AACTGGGCAT GCCGAAGACC AAACGCACCA 60

AGACCGGCTA CACCACGGAT GCCGACGCGC TGCAGTCGTT GTTCGACAAG ACCGGGCATC 120

CGTTTCTGCA ACATCTGCTC GCCCACCGCG ACGTCACCCG GCTCAAGGTC ACCGTCGACG 180

GGTTGCTCCA AGCGGTGGCC GCCGACGGCC GCATCCACAC CACGTTCAAC CAGACGATCG 240

CCGCGACCGG CCGGCTCTCC TCGACCGAAC CCAACCTGCA GAACATCCCG ATCCGCACCG 300

ACGCGGGCCG GCGGATCCGG GACGCGTTCG TGGTCGGGGA CGGTTACGCC GAGTTGATGA 360

CGGCCGACTA CAGCCAGATC GAGATGCGGA TCATGGGGCA CCTGTCCGGG GACGAGGGCC 420

TCATCGAGGC GTTCAACACC GGGGAGGACC TGTATTCGTT CGTCGCGTCC CGGGTGTTCG 480

GTGTGCCCAT CGACGAGGTC ACCGGCGAGT TGCGGCGCCG GGTCAAGGCG ATGTCCTACG 540

GGCTGGTTTA CGGGTTGAGC GCCTACGGCC TGTCGCAGCA GTTGAAAATC TCCACCGAGG 600

AAGCCAACGA GCAGATGGAC GCGTATTTCG CCCGATTCGG CGGGGTGCGC GACTACCTGC 660

GCGCCGTAGT CGAGCGGGCC CGCAAGGACG GCTACACCTC GACGGTGCTG GGCCGTCGCC 720

GCTACCTGCC CGAGCTGGAC AGCAGCAACC GTCAAGTGCG GGAGGCCGCC GAGCGGGCGG 780

CGCTGAACGC GCCGATCCAG GGCAGCGCGG CCGACATCAT CAAGGTGGCC ATGATCCAGG 840

TCGACAAGGC GCTCAACGAG GCACAGCTGG CGTCGCGCAT GCTGCTGCAG GTCCACGACG 900

AGCTGCTGTT CGAAATCGCC CCCGGTGAAC GCGAGCGGGT CGAGGCCCTG GTGCGCGACA 960

AGATGGGCGG CGCTTACCCG CTCGACGTCC CGCTGGAGGT GTCGGTGGGC TACGGCCGCA 1020

GCTGGGACGC GGCGGCGCAC TGAGTGCCGA GCGTGCATCT GGGGCGGGAA TTCGGCGATT 1080

TTTCCGCCCT GAGTTCACGC TCGGCGCAAT CGGGACCGAG TTTGTCCAGC GTGTACCCGT 1140

CGAGTAGCCT CGTCA 1155

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1771 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGCGCCGTC TGGTGTTTGA ACGGTTTTAC CGGTCGGCAT CGGCACGGGC GTTGCCGGGT 60

TCGGGCCTCG GGTTGGCGAT CGTCAAACAG GTGGTGCTCA ACCACGGCGG ATTGCTGCGC 120

ATCGAAGACA CCGACCCAGG CGGCCAGCCC CCTGGAACGT CGATTTACGT GCTGCTCCCC 180

GGCCGTCGGA TGCCGATTCC GCAGCTTCCC GGTGCGACGG CTGGCGCTCG GAGCACGGAC 240

ATCGAGAACT CTCGGGGTTC GGCGAACGTT ATCTCAGTGG AATCTCAGTC CACGCGCGCA 300

ACCTAGTTGT GCAGTTACTG TTGAAAGCCA CACCCATGCC AGTCCACGCA TGGCCAAGTT 360

GGCCCGAGTA GTGGGCCTAG TACAGGAAGA GCAACCTAGC GACATGACGA ATCACCCACG 420

GTATTCGCCA CCGCCGCAGC AGCCGGGAAC CCCAGGTTAT GCTCAGGGGC AGCAGCAAAC 480

GTACAGCCAG CAGTTCGACT GGCGTTACCC ACCGTCCCCG CCCCCGCAGC CAACCCAGTA 540

CCGTCAACCC TACGAGGCGT TGGGTGGTAC CCGGCCGGGT CTGATACCTG GCGTGATTCC 600

GACCATGACG CCCCCTCCTG GGATGGTTCG CCAACGCCCT CGTGCAGGCA TGTTGGCCAT 660

CGGCGCGGTG ACGATAGCGG TGGTGTCCGC CGGCATCGGC GGCGCGGCCG CATCCCTGGT 720

CGGGTTCAAC CGGGCACCCG CCGGCCCCAG CGGCGGCCCA GTGGCTGCCA GCGCGGCGCC 780

AAGCATCCCC GCAGCAAACA TGCCGCCGGG GTCGGTCGAA CAGGTGGCGG CCAAGGTGGT 840

GCCCAGTGTC GTCATGTTGG AAACCGATCT GGGCCGCCAG TCGGAGGAGG GCTCCGGCAT 900

CATTCTGTCT GCCGAGGGGC TGATCTTGAC CAACAACCAC GTGATCGCGG CGGCCGCCAA 960

GCCTCCCCTG GGCAGTCCGC CGCCGAAAAC GACGGTAACC TTCTCTGACG GGCGGACCGC 1020

ACCCTTCACG GTGGTGGGGG CTGACCCCAC CAGTGATATC GCCGTCGTCC GTGTTCAGGG 1080

CGTCTCCGGG CTCACCCCGA TCTCCCTGGG TTCCTCCTCG GACCTGAGGG TCGGTCAGCC 1140

GGTGCTGGCG ATCGGGTCGC CGCTCGGTTT GGAGGGCACC GTGACCACGG GGATCGTCAG 1200

CGCTCTCAAC CGTCCAGTGT CGACGACCGG CGAGGCCGGC AACCAGAACA CCGTGCTGGA 1260

CGCCATTCAG ACCGACGCCG CGATCAACCC CGGTAACTCC GGGGGCGCGC TGGTGAACAT 1320

GAACGCTCAA CTCGTCGGAG TCAACTCGGC CATTGCCACG CTGGGCGCGG ACTCAGCCGA 1380

TGCGCAGAGC GGCTCGATCG GTCTCGGTTT TGCGATTCCA GTCGACCAGG CCAAGCGCAT 1440

CGCCGACGAG TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC 1500

CAATGACAAA GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC 1560

GAACGCTGGA GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG 1620

CGCGGACGCG TTGGTTGCCG CCGTGCGGTC CAAAGCGCCG GGCGCCACGG TGGCGCTAAC 1680

CTTTCAGGAT CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA 1740

GTGATGAAGG TCGCCGCGCA GTGTTCAAAG C 1771

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1058 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTCCACCGCG GTGGCGGCCG CTCTAGAACT AGTGGATCCC CCGGGCTGCA GGAATTCGGC 60

ACGAGGATCC GACGTCGCAG GTTGTCGAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT 120

AGCCCGGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCGGGCAAT TTGGCGGGGC 180

CCGGCGACGG CGAGCGCCGG AATGGCGCGA GTGAGGAGGC GGGCAGTCAT GCCCAGCGTG 240

ATCCAATCAA CCTGCATTCG GCCTGCGGGC CCATTTGACA ATCGAGGTAG TGAGCGCAAA 300

TGAATGATGG AAAACGGGCG GTGACGTCCG CTGTTCTGGT GGTGCTAGGT GCCTGCCTGG 360

CGTTGTGGCT ATCAGGATGT TCTTCGCCGA AACCTGATGC CGAGGAACAG GGTGTTCCCG 420

TGAGCCCGAC GGCGTCCGAC CCCGCGCTCC TCGCCGAGAT CAGGCAGTCG CTTGATGCGA 480

CAAAAGGGTT GACCAGCGTG CACGTAGCGG TCCGAACAAC CGGGAAAGTC GACAGCTTGC 540

TGGGTATTAC CAGTGCCGAT GTCGACGTCC GGGCCAATCC GCTCGCGGCA AAGGGCGTAT 600

GCACCTACAA CGACGAGCAG GGTGTCCCGT TTCGGGTACA AGGCGACAAC ATCTCGGTGA 660

AACTGTTCGA CGACTGGAGC AATCTCGGCT CGATTTCTGA ACTGTCAACT TCACGCGTGC 720

TCGATCCTGC CGCTGGGGTG ACGCAGCTGC TGTCCGGTGT CACGAACCTC CAAGCGCAAG 780

GTACCGAAGT GATAGACGGA ATTTCGACCA CCAAAATCAC CGGGACCATC CCCGCGAGCT 840

CTGTCAAGAT GCTTGATCCT GGCGCCAAGA GTGCAAGGCC GGCGACCGTG TGGATTGCCC 900

AGGACGGCTC GCACCACCTC GTCCGAGCGA GCATCGACCT CGGATCCGGG TCGATTCAGC 960

TCACGCAGTC GAAATGGAAC GAACCCGTCA ACGTCGACTA GGCCGAAGTT GCGTCGACGC 1020

GTTGNTCGAA ACGCCCTTGT GAACGGTGTC AACGGNAC 1058

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 542 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTCGGCA CGAGAGGTGA TCGACATCAT CGGGACCAGC CCCACATCCT GGGAACAGGC 60

GGCGGCGGAG GCGGTCCAGC GGGCGCGGGA TAGCGTCGAT GACATCCGCG TCGCTCGGGT 120

CATTGAGCAG GACATGGCCG TGGACAGCGC CGGCAAGATC ACCTACCGCA TCAAGCTCGA 180

AGTGTCGTTC AAGATGAGGC CGGCGCAACC GCGCTAGCAC GGGCCGGCGA GCAAGACGCA 240

AAATCGCACG GTTTGCGGTT GATTCGTGCG ATTTTGTGTC TGCTCGCCGA GGCCTACCAG 300

GCGCGGCCCA GGTCCGCGTG CTGCCGTATC CAGGCGTGCA TCGCGATTCC GGCGGCCACG 360

CCGGAGTTAA TGCTTCGCGT CGACCCGAAC TGGGCGATCC GCCGGNGAGC TGATCGATGA 420

CCGTGGCCAG CCCGTCGATG CCCGAGTTGC CCGAGGAAAC GTGCTGCCAG GCCGGTAGGA 480

AGCGTCCGTA GGCGGCGGTG CTGACCGGCT CTGCCTGCGC CCTCAGTGCG GCCAGCGAGC 540

GG 542

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 913 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGTGCCGCC CGCGCCTCCG TTGCCCCCAT TGCCGCCGTC GCCGATCAGC TGCGCATCGC 60

CACCATCACC GCCTTTGCCG CCGGCACCGC CGGTGGCGCC GGGGCCGCCG ATGCCACCGC 120

TTGACCCTGG CCGCCGGCGC CGCCATTGCC ATACAGCACC CCGCCGGGGG CACCGTTACC 180

GCCGTCGCCA CCGTCGCCGC CGCTGCCGTT TCAGGCCGGG GAGGCCGAAT GAACCGCCGC 240

CAAGCCCGCC GCCGGCACCG TTGCCGCCTT TTCCGCCCGC CCCGCCGGCG CCGCCAATTG 300

CCGAACAGCC AMGCACCGTT GCCGCCAGCC CCGCCGCCGT TAACGGCGCT GCCGGGCGCC 360

GCCGCCGGAC CCGCCATTAC CGCCGTTCCC GTTCGGTGCC CCGCCGTTAC CGGCGCCGCC 420

GTTTGCCGCC AATATTCGGC GGGCACCGCC AGACCCGCCG GGGCCACCAT TGCCGCCGGG 480

CACCGAAACA ACAGCCCAAC GGTGCCGCCG GCCCCGCCGT TTGCCGCCAT CACCGGCCAT 540

TCACCGCCAG CACCGCCGTT AATGTTTATG AACCCGGTAC CGCCAGCGCG GCCCCTATTG 600

CCGGGCGCCG GAGNGCGTGC CCGCCGGCGC CGCCAACGCC CAAAAGCCCG GGGTTGCCAC 660

CGGCCCCGCC GGACCCACCG GTCCCGCCGA TCCCCCCGTT GCCGCCGGTG CCGCCGCCAT 720

TGGTGCTGCT GAAGCCGTTA GCGCCGGTTC CGCSGGTTCC GGCGGTGGCG CCNTGGCCGC 780

CGGCCCCGCC GTTGCCGTAC AGCCACCCCC CGGTGGCGCC GTTGCCGCCA TTGCCGCCAT 840

TGCCGCCGTT GCCGCCATTG CCGCCGTTCC CGCCGCCACC GCCGGNTTGG CCGCCGGCGC 900

CGCCGGCGGC CGC 913

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1872 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GACTACGTTG GTGTAGAAAA ATCCTGCCGC CCGGACCCTT AAGGCTGGGA CAATTTCTGA 60

TAGCTACCCC GACACAGGAG GTTACGGGAT GAGCAATTCG CGCCGCCGCT CACTCAGGTG 120

GTCATGGTTG CTGAGCGTGC TGGCTGCCGT CGGGCTGGGC CTGGCCACGG CGCCGGCCCA 180

GGCGGCCCCG CCGGCCTTGT CGCAGGACCG GTTCGCCGAC TTCCCCGCGC TGCCCCTCGA 240

CCCGTCCGCG ATGGTCGCCC AAGTGGCGCC ACAGGTGGTC AACATCAACA CCAAACTGGG 300

CTACAACAAC GCCGTGGGCG CCGGGACCGG CATCGTCATC GATCCCAACG GTGTCGTGCT 360

GACCAACAAC CACGTGATCG CGGGCGCCAC CGACATCAAT GCGTTCAGCG TCGGCTCCGG 420

CCAAACCTAC GGCGTCGATG TGGTCGGGTA TGACCGCACC CAGGATGTCG CGGTGCTGCA 480

GCTGCGCGGT GCCGGTGGCC TGCCGTCGGC GGCGATCGGT GGCGGCGTCG CGGTTGGTGA 540

GCCCGTCGTC GCGATGGGCA ACAGCGGTGG GCAGGGCGGA ACGCCCCGTG CGGTGCCTGG 600

CAGGGTGGTC GCGCTCGGCC AAACCGTGCA GGCGTCGGAT TCGCTGACCG GTGCCGAAGA 660

GACATTGAAC GGGTTGATCC AGTTCGATGC CGCAATCCAG CCCGGTGATT CGGGCGGGCC 720

CGTCGTCAAC GGCCTAGGAC AGGTGGTCGG TATGAACACG GCCGCGTCCG ATAACTTCCA 780

GCTGTCCCAG GGTGGGCAGG GATTCGCCAT TCCGATCGGG CAGGCGATGG CGATCGCGGG 840

CCAAATCCGA TCGGGTGGGG GGTCACCCAC CGTTCATATC GGGCCTACCG CCTTCCTCGG 900

CTTGGGTGTT GTCGACAACA ACGGCAACGG CGCACGAGTC CAACGCGTGG TCGGAAGCGC 960

TCCGGCGGCA AGTCTCGGCA TCTCCACCGG CGACGTGATC ACCGCGGTCG ACGGCGCTCC 1020

GATCAACTCG GCCACCGCGA TGGCGGACGC GCTTAACGGG CATCATCCCG GTGACGTCAT 1080

CTCGGTGAAC TGGCAAACCA AGTCGGGCGG CACGCGTACA GGGAACGTGA CATTGGCCGA 1140

GGGACCCCCG GCCTGATTTG TCGCGGATAC CACCCGCCGG CCGGCCAATT GGATTGGCGC 1200

CAGCCGTGAT TGCCGCGTGA GCCCCCGAGT TCCGTCTCCC GTGCGCGTGG CATTGTGGAA 1260

GCAATGAACG AGGCAGAACA CAGCGTTGAG CACCCTCCCG TGCAGGGCAG TTACGTCGAA 1320

GGCGGTGTGG TCGAGCATCC GGATGCCAAG GACTTCGGCA GCGCCGCCGC CCTGCCCGCC 1380

GATCCGACCT GGTTTAAGCA CGCCGTCTTC TACGAGGTGC TGGTCCGGGC GTTCTTCGAC 1440

GCCAGCGCGG ACGGTTCCGN CGATCTGCGT GGACTCATCG ATCGCCTCGA CTACCTGCAG 1500

TGGCTTGGCA TCGACTGCAT CTGTTGCCGC CGTTCCTACG ACTCACCGCT GCGCGACGGC 1560

GGTTACGACA TTCGCGACTT CTACAAGGTG CTGCCCGAAT TCGGCACCGT CGACGATTTC 1620

GTCGCCCTGG TCGACACCGC TCACCGGCGA GGTATCCGCA TCATCACCGA CCTGGTGATG 1680

AATCACACCT CGGAGTCGCA CCCCTGGTTT CAGGAGTCCC GCCGCGACCC AGACGGACCG 1740

TACGGTGACT ATTACGTGTG GAGCGACACC AGCGAGCGCT ACACCGACGC CCGGATCATC 1800

TTCGTCGACA CCGAAGAGTC GAACTGGTCA TTCGATCCTG TCCGCCGACA GTTNCTACTG 1860

GCACCGATTC TT 1872

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1482 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTTCGCCGAA ACCTGATGCC GAGGAACAGG GTGTTCCCGT GAGCCCGACG GCGTCCGACC 60

CCGCGCTCCT CGCCGAGATC AGGCAGTCGC TTGATGCGAC AAAAGGGTTG ACCAGCGTGC 120

ACGTAGCGGT CCGAACAACC GGGAAAGTCG ACAGCTTGCT GGGTATTACC AGTGCCGATG 180

TCGACGTCCG GGCCAATCCG CTCGCGGCAA AGGGCGTATG CACCTACAAC GACGAGCAGG 240

GTGTCCCGTT TCGGGTACAA GGCGACAACA TCTCGGTGAA ACTGTTCGAC GACTGGAGCA 300

ATCTCGGCTC GATTTCTGAA CTGTCAACTT CACGCGTGCT CGATCCTGCC GCTGGGGTGA 360

CGCAGCTGCT GTCCGGTGTC ACGAACCTCC AAGCGCAAGG TACCGAAGTG ATAGACGGAA 420

TTTCGACCAC CAAAATCACC GGGACCATCC CCGCGAGCTC TGTCAAGATG CTTGATCCTG 480

GCGCCAAGAG TGCAAGGCCG GCGACCGTGT GGATTGCCCA GGACGGCTCG CACCACCTCG 540

TCCGAGCGAG CATCGACCTC GGATCCGGGT CGATTCAGCT CACGCAGTCG AAATGGAACG 600

AACCCGTCAA CGTCGACTAG GCCGAAGTTG CGTCGACGCG TTGCTCGAAA CGCCCTTGTG 660

AACGGTGTCA ACGGCACCCG AAAACTGACC CCCTGACGGC ATCTGAAAAT TGACCCCCTA 720

GACCGGGCGG TTGGTGGTTA TTCTTCGGTG GTTCCGGCTG GTGGGACGCG GCCGAGGTCG 780

CGGTCTTTGA GCCGGTAGCT GTCGCCTTTG AGGGCGACGA CTTCAGCATG GTGGACGAGG 840

CGGTCGATCA TGGCGGCAGC AACGACGTCG TCGCCGCCGA AAACCTCGCC CCACCGGCCG 900

AAGGCCTTAT TGGACGTGAC GATCAAGCTG GCCCGCTCAT ACCGGGAGGA CACCAGCTGG 960

AAGAAGAGGT TGGCGGCCTC GGGCTCAAAC GGAATGTAAC CGACTTCGTC AACCACCAGG 1020

AGCGGATAGC GGCCAAACCG GGTGAGTTCG GCGTAGATGC GCCCGGCGTG GTGAGCCTCG 1080

GCGAACCGTG CTACCCATTC GGCGGCGGTG GCGAACAGCA CCCGATGACC GGCCTGACAC 1140

GCGCGTATCG CCAGGCCGAC CGCAAGATGA GTCTTCCCGG TGCCAGGCGG GGCCCAAAAA 1200

CACGACGTTA TCGCGGGCGG TGATGAAATC CAGGGTGCCC AGATGTGCGA TGGTGTCGCG 1260

TTTGAGGCCA CGAGCATGCT CAAAGTCGAA CTCTTCCAAC GACTTCCGAA CCGGGAAGCG 1320

GGCGGCGCGG ATGCGGCCCT CACCACCATG GGACTCCCGG GCTGACACTT CCCGCTGCAG 1380

GCAGGCGGCC AGGTATTCTT CGTGGCTCCA GTTCTCGGCG CGGGCGCGAT CGGCCAGCCG 1440

GGACACTGAC TCACGCAGGG TGGGAGCTTT CAATGCTCTT GT 1482

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 876 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCGGCA CGAGCCGGCG ATAGCTTCTG GGCCGCGGCC GACCAGATGG CTCGAGGGTT 60

CGTGCTCGGG GCCACCGCCG GGCGCACCAC CCTGACCGGT GAGGGCCTGC AACACGCCGA 120

CGGTCACTCG TTGCTGCTGG ACGCCACCAA CCCGGCGGTG GTTGCCTACG ACCCGGCCTT 180

CGCCTACGAA ATCGGCTACA TCGNGGAAAG CGGACTGGCC AGGATGTGCG GGGAGAACCC 240

GGAGAACATC TTCTTCTACA TCACCGTCTA CAACGAGCCG TACGTGCAGC CGCCGGAGCC 300

GGAGAACTTC GATCCCGAGG GCGTGCTGGG GGGTATCTAC CGNTATCACG CGGCCACCGA 360

GCAACGCACC AACAAGGNGC AGATCCTGGC CTCCGGGGTA GCGATGCCCG CGGCGCTGCG 420

GGCAGCACAG ATGCTGGCCG CCGAGTGGGA TGTCGCCGCC GACGTGTGGT CGGTGACCAG 480

TTGGGGCGAG CTAAACCGCG ACGGGGTGGT CATCGAGACC GAGAAGCTCC GCCACCCCGA 540

TCGGCCGGCG GGCGTGCCCT ACGTGACGAG AGCGCTGGAG AATGCTCGGG GCCCGGTGAT 600

CGCGGTGTCG GACTGGATGC GCGCGGTCCC CGAGCAGATC CGACCGTGGG TGCCGGGCAC 660

ATACCTCACG TTGGGCACCG ACGGGTTCGG TTTTTCCGAC ACTCGGCCCG CCGGTCGTCG 720

TTACTTCAAC ACCGACGCCG AATCCCAGGT TGGTCGCGGT TTTGGGAGGG GTTGGCCGGG 780

TCGACGGGTG AATATCGACC CATTCGGTGC CGGTCGTGGG CCGCCCGCCC AGTTACCCGG 840

ATTCGACGAA GGTGGGGGGT TGCGCCCGAN TAAGTT 876

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1021 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATCCCCCCGG GCTGCAGGAA TTCGGCACGA GAGACAAAAT TCCACGCGTT AATGCAGGAA 60

CAGATTCATA ACGAATTCAC AGCGGCACAA CAATATGTCG CGATCGCGGT TTATTTCGAC 120

AGCGAAGACC TGCCGCAGTT GGCGAAGCAT TTTTACAGCC AAGCGGTCGA GGAACGAAAC 180

CATGCAATGA TGCTCGTGCA ACACCTGCTC GACCGCGACC TTCGTGTCGA AATTCCCGGC 240

GTAGACACGG TGCGAAACCA GTTCGACAGA CCCCGCGAGG CACTGGCGCT GGCGCTCGAT 300

CAGGAACGCA CAGTCACCGA CCAGGTCGGT CGGCTGACAG CGGTGGCCCG CGACGAGGGC 360

GATTTCCTCG GCGAGCAGTT CATGCAGTGG TTCTTGCAGG AACAGATCGA AGAGGTGGCC 420

TTGATGGCAA CCCTGGTGCG GGTTGCCGAT CGGGCCGGGG CCAACCTGTT CGAGCTAGAG 480

AACTTCGTCG CACGTGAAGT GGATGTGGCG CCGGCCGCAT CAGGCGCCCC GCACGCTGCC 540

GGGGGCCGCC TCTAGATCCC TGGGGGGGAT CAGCGAGTGG TCCCGTTCGC CCGCCCGTCT 600

TCCAGCCAGG CCTTGGTGCG GCCGGGGTGG TGAGTACCAA TCCAGGCCAC CCCGACCTCC 660

CGGNAAAAGT CGATGTCCTC GTACTCATCG ACGTTCCAGG AGTACACCGC CCGGCCCTGA 720

GCTGCCGAGC GGTCAACGAG TTGCGGATAT TCCTTTAACG CAGGCAGTGA GGGTCCCACG 780

GCGGTTGGCC CGACCGCCGT GGCCGCACTG CTGGTCAGGT ATCGGGGGGT CTTGGCGAGC 840

AACAACGTCG GCAGGAGGGG TGGAGCCCGC CGGATCCGCA GACCGGGGGG GCGAAAACGA 900

CATCAACACC GCACGGGATC GATCTGCGGA GGGGGGTGCG GGAATACCGA ACCGGTGTAG 960

GAGCGCCAGC AGTTGTTTTT CCACCAGCGA AGCGTTTTCG GGTCATCGGN GGCNNTTAAG 1020

T 1021

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 321 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGTGCCGACG AACGGAAGAA CACAACCATG AAGATGGTGA AATCGATCGC CGCAGGTCTG 60

ACCGCCGCGG CTGCAATCGG CGCCGCTGCG GCCGGTGTGA CTTCGATCAT GGCTGGCGGN 120

CCGGTCGTAT ACCAGATGCA GCCGGTCGTC TTCGGCGCGC CACTGCCGTT GGACCCGGNA 180

TCCGCCCCTG ANGTCCCGAC CGCCGCCCAG TGGACCAGNC TGCTCAACAG NCTCGNCGAT 240

CCCAACGTGT CGTTTGNGAA CAAGGGNAGT CTGGTCGAGG GNGGNATCGG NGGNANCGAG 300

GGNGNGNATC GNCGANCACA A 321

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 373 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TCTTATCGGT TCCGGTTGGC GACGGGTTTT GGGNGCGGGT GGTTAACCCG CTCGGCCAGC 60

CGATCGACGG GCGCGGAGAC GTCGACTCCG ATACTCGGCG CGCGCTGGAG CTCCAGGCGC 120

CCTCGGTGGT GNACCGGCAA GGCGTGAAGG AGCCGTTGNA GACCGGGATC AAGGCGATTG 180

ACGCGATGAC CCCGATCGGC CGCGGGCAGC GCCAGCTGAT CATCGGGGAC CGCAAGACCG 240

GCAAAAACCG CCGTCTGTGT CGGACACCAT CCTCAAACCA GCGGGAAGAA CTGGGAGTCC 300

GGTGGATCCC AAGAAGCAGG TGCGCTTGTG TATACGTTGG CCATCGGGCA AGAAGGGGAA 360

CTTACCATCG CCG 373

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 352 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTGACGCCGT GATGGGATTC CTGGGCGGGG CCGGTCCGCT GGCGGTGGTG GATCAGCAAC 60

TGGTTACCCG GGTGCCGCAA GGCTGGTCGT TTGCTCAGGC AGCCGCTGTG CCGGTGGTGT 120

TCTTGACGGC CTGGTACGGG TTGGCCGATT TAGCCGAGAT CAAGGCGGGC GAATCGGTGC 180

TGATCCATGC CGGTACCGGC GGTGTGGGCA TGGCGGCTGT GCAGCTGGCT CGCCAGTGGG 240

GCGTGGAGGT TTTCGTCACC GCCAGCCGTG GNAAGTGGGA CACGCTGCGC GCCATNGNGT 300

TTGACGACGA NCCATATCGG NGATTCCCNC ACATNCGAAG TTCCGANGGA GA 352

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 726 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GAAATCCGCG TTCATTCCGT TCGACCAGCG GCTGGCGATA ATCGACGAAG TGATCAAGCC 60

GCGGTTCGCG GCGCTCATGG GTCACAGCGA GTAATCAGCA AGTTCTCTGG TATATCGCAC 120

CTAGCGTCCA GTTGCTTGCC AGATCGCTTT CGTACCGTCA TCGCATGTAC CGGTTCGCGT 180

GCCGCACGCT CATGCTGGCG GCGTGCATCC TGGCCACGGG TGTGGCGGGT CTCGGGGTCG 240

GCGCGCAGTC CGCAGCCCAA ACCGCGCCGG TGCCCGACTA CTACTGGTGC CCGGGGCAGC 300

CTTTCGACCC CGCATGGGGG CCCAACTGGG ATCCCTACAC CTGCCATGAC GACTTCCACC 360

GCGACAGCGA CGGCCCCGAC CACAGCCGCG ACTACCCCGG ACCCATCCTC GAAGGTCCCG 420

TGCTTGACGA TCCCGGTGCT GCGCCGCCGC CCCCGGCTGC CGGTGGCGGC GCATAGCGCT 480

CGTTGACCGG GCCGCATCAG CGAATACGCG TATAAACCCG GGCGTGCCCC CGGCAAGCTA 540

CGACCCCCGG CGGGGCAGAT TTACGCTCCC GTGCCGATGG ATCGCGCCGT CCGATGACAG 600

AAAATAGGCG ACGGTTTTGG CAACCGCTTG GAGGACGCTT GAAGGGAACC TGTCATGAAC 660

GGCGACAGCG CCTCCACCAT CGACATCGAC AAGGTTGTTA CCCGCACACC CGTTCGCCGG 720

ATCGTG 726

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 580 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGCGACGACG ACGAACGTCG GGCCCACCAC CGCCTATGCG TTGATGCAGG CGACCGGGAT 60

GGTCGCCGAC CATATCCAAG CATGCTGGGT GCCCACTGAG CGACCTTTTG ACCAGCCGGG 120

CTGCCCGATG GCGGCCCGGT GAAGTCATTG CGCCGGGGCT TGTGCACCTG ATGAACCCGA 180

ATAGGGAACA ATAGGGGGGT GATTTGGCAG TTCAATGTCG GGTATGGCTG GAAATCCAAT 240

GGCGGGGCAT GCTCGGCGCC GACCAGGCTC GCGCAGGCGG GCCAGCCCGA ATCTGGAGGG 300

AGCACTCAAT GGCGGCGATG AAGCCCCGGA CCGGCGACGG TCCTTTGGAA GCAACTAAGG 360

AGGGGCGCGG CATTGTGATG CGAGTACCAC TTGAGGGTGG CGGTCGCCTG GTCGTCGAGC 420

TGACACCCGA CGAAGCCGCC GCACTGGGTG ACGAACTCAA AGGCGTTACT AGCTAAGACC 480

AGCCCAACGG CGAATGGTCG GCGTTACGCG CACACCTTCC GGTAGATGTC CAGTGTCTGC 540

TCGGCGATGT ATGCCCAGGA GAACTCTTGG ATACAGCGCT 580

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AACGGAGGCG CCGGGGGTTT TGGCGGGGCC GGGGCGGTCG GCGGCAACGG CGGGGCCGGC 60

GGTACCGCCG GGTTGTTCGG TGTCGGCGGG GCCGGTGGGG CCGGAGGCAA CGGCATCGCC 120

GGTGTCACGG GTACGTCGGC CAGCACACCG GGTGGATCCG 160

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 272 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GACACCGATA CGATGGTGAT GTACGCCAAC GTTGTCGACA CGCTCGAGGC GTTCACGATC 60

CAGCGCACAC CCGACGGCGT GACCATCGGC GATGCGGCCC CGTTCGCGGA GGCGGCTGCC 120

AAGGCGATGG GAATCGACAA GCTGCGGGTA ATTCATACCG GAATGGACCC CGTCGTCGCT 180

GAACGCGAAC AGTGGGACGA CGGCAACAAC ACGTTGGCGT TGGCGCCCGG TGTCGTTGTC 240

GCCTACGAGC GCAACGTACA GACCAACGCC CG 272

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 317 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GCAGCCGGTG GTTCTCGGAC TATCTGCGCA CGGTGACGCA GCGCGACGTG CGCGAGCTGA 60

AGCGGATCGA GCAGACGGAT CGCCTGCCGC GGTTCATGCG CTACCTGGCC GCTATCACCG 120

CGCAGGAGCT GAACGTGGCC GAAGCGGCGC GGGTCATCGG GGTCGACGCG GGGACGATCC 180

GTTCGGATCT GGCGTGGTTC GAGACGGTCT ATCTGGTACA TCGCCTGCCC GCCTGGTCGC 240

GGAATCTGAC CGCGAAGATC AAGAAGCGGT CAAAGATCCA CGTCGTCGAC AGTGGCTTCG 300

CGGCCTGGTT GCGCGGG 317

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 182 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GATCGTGGAG CTGTCGATGA ACAGCGTTGC CGGACGCGCG GCGGCCAGCA CGTCGGTGTA 60

GCAGCGCCGG ACCACCTCGC CGGTGGGCAG CATGGTGATG ACCACGTCGG CCTCGGCCAC 120

CGCTTCGGGC GCGCTACGAA ACACCGCGAC ACCGTGCGCG GCGGCGCCGG ACGCCGCCGT 180

GG 182

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 308 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GATCGCGAAG TTTGGTGAGC AGGTGGTCGA CGCGAAAGTC TGGGCGCCTG CGAAGCGGGT 60

CGGCGTTCAC GAGGCGAAGA CACGCCTGTC CGAGCTGCTG CGGCTCGTCT ACGGCGGGCA 120

GAGGTTGAGA TTGCCCGCCG CGGCGAGCCG GTAGCAAAGC TTGTGCCGCT GCATCCTCAT 180

GAGACTCGGC GGTTAGGCAT TGACCATGGC GTGTACCGCG TGCCCGACGA TTTGGACGCT 240

CCGTTGTCAG ACGACGTGCT CGAACGCTTT CACCGGTGAA GCGCTACCTC ATCGACACCC 300

ACGTTTGG 308

(2) INFORMATION FOR SEQ ID NO:31:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 267 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CCGACGACGA GCAACTCACG TGGATGATGG TCGGCAGCGG CATTGAGGAC GGAGAGAATC 60

CGGCCGAAGC TGCCGCGCGG CAAGTGCTCA TAGTGACCGG CCGTAGAGGG CTCCCCCGAT 120

GGCACCGGAC TATTCTGGTG TGCCGCTGGC CGGTAAGAGC GGGTAAAAGA ATGTGAGGGG 180

ACACGATGAG CAATCACACC TACCGAGTGA TCGAGATCGT CGGGACCTCG CCCGACGGCG 240

TCGACGCGGC AATCCAGGGC GGTCTGG 267

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 189 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CTCGTGCCGA AAGAATGTGA GGGGACACGA TGAGCAATCA CACCTACCGA GTGATCGAGA 60

TCGTCGGGAC CTCGCCCGAC GGCGTCGACG CGGCAATCCA GGGCGGTCTG GCCCGAGCTG 120

CGCAGACCAT GCGCGCGCTG GACTGGTTCG AAGTACAGTC AATTCGAGGC CACCTGGTCG 180

ACGGAGCGG 189

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 851 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTGCAGGGTG GCGTGGATGA GCGTCACCGC GGGGCAGGCC GAGCTGACCG CCGCCCAGGT 60

CCGGGTTGCT GCGGCGGCCT ACGAGACGGC GTATGGGCTG ACGGTGCCCC CGCCGGTGAT 120

CGCCGAGAAC CGTGCTGAAC TGATGATTCT GATAGCGACC AACCTCTTGG GGCAAAACAC 180

CCCGGCGATC GCGGTCAACG AGGCCGAATA CGGCGAGATG TGGGCCCAAG ACGCCGCCGC 240

GATGTTTGGC TACGCCGCGG CGACGGCGAC GGCGACGGCG ACGTTGCTGC CGTTCGAGGA 300

GGCGCCGGAG ATGACCAGCG CGGGTGGGCT CCTCGAGCAG GCCGCCGCGG TCGAGGAGGC 360

CTCCGACACC GCCGCGGCGA ACCAGTTGAT GAACAATGTG CCCCAGGCGC TGAAACAGTT 420

GGCCCAGCCC ACGCAGGGCA CCACGCCTTC TTCCAAGCTG GGTGGCCTGT GGAAGACGGT 480

CTCGCCGCAT CGGTCGCCGA TCAGCAACAT GGTGTCGATG GCCAACAACC ACATGTCGAT 540

GACCAACTCG GGTGTGTCGA TGACCAACAC CTTGAGCTCG ATGTTGAAGG GCTTTGCTCC 600

GGCGGCGGCC GCCCAGGCCG TGCAAACCGC GGCGCAAAAC GGGGTCCGGG CGATGAGCTC 660

GCTGGGCAGC TCGCTGGGTT CTTCGGGTCT GGGCGGTGGG GTGGCCGCCA ACTTGGGTCG 720

GGCGGCCTCG GTACGGTATG GTCACCGGGA TGGCGGAAAA TATGCANAGT CTGGTCGGCG 780

GAACGGTGGT CCGGCGTAAG GTTTACCCCC GTTTTCTGGA TGCGGTGAAC TTCGTCAACG 840

GAAACAGTTA C 851

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 254 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GATCGATCGG GCGGAAATTT GGACCAGATT CGCCTCCGGC GATAACCCAA TCAATCGAAC 60

CTAGATTTAT TCCGTCCAGG GGCCCGAGTA ATGGCTCGCA GGAGAGGAAC CTTACTGCTG 120

CGGGCACCTG TCGTAGGTCC TCGATACGGC GGAAGGCGTC GACATTTTCC ACCGACACCC 180

CCATCCAAAC GTTCGAGGGC CACTCCAGCT TGTGAGCGAG GCGACGCAGT CGCAGGCTGC 240

GCTTGGTCAA GATC 254

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 408 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CGGCACGAGG ATCCTGACCG AAGCGGCCGC CGCCAAGGCG AAGTCGCTGT TGGACCAGGA 60

GGGACGGGAC GATCTGGCGC TGCGGATCGC GGTTCAGCCG GGGGGGTGCG CTGGATTGCG 120

CTATAACCTT TTCTTCGACG ACCGGACGCT GGATGGTGAC CAAACCGCGG AGTTCGGTGG 180

TGTCAGGTTG ATCGTGGACC GGATGAGCGC GCCGTATGTG GAAGGCGCGT CGATCGATTT 240

CGTCGACACT ATTGAGAAGC AAGGNTTCAC CATCGACAAT CCCAACGCCA CCGGCTCCTG 300

CGCGTGCGGG GATTCGTTCA ACTGATAAAA CGCTAGTACG ACCCCGCGGT GCGCAACACG 360

TACGAGCACA CCAAGACCTG ACCGCGCTGG AAAAGCAACT GAGCGATG 408

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 181 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGGGCCGGC GGGGCCGGCG 60

GGACCGGCGC TAACGGTGGT GCCGGCGGCA ACGCCTGGTT GTTCGGGGCC GGCGGGTCCG 120

GCGGNGCCGG CACCAATGGT GGNGTCGGCG GGTCCGGCGG ATTTGTCTAC GGCAACGGCG 180

G 181

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 290 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGTGTCGGC GGCCGGGGCG 60

GCGACGGCGT CTTTGCCGGT GCCGGCGGCC AGGGCGGCCT CGGTGGGCAG GGCGGCAATG 120

GCGGCGGCTC CACCGGCGGC AACGGCGGTC TTGGCGGCGC GGGCGGTGGC GGAGGCAACG 180

CCCCGGACGG CGGCTTCGGT GGCAACGGCG GTAAGGGTGG CCAGGGCGGN ATTGGCGGCG 240

GCACTCAGAG CGCGACCGGC CTCGGNGGTG ACGGCGGTGA CGGCGGTGAC 290

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GATCCAGTGG CATGGNGGGT GTCAGTGGAA GCAT 34

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 155 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GATCGCTGCT CGTCCCCCCC TTGCCGCCGA CGCCACCGGT CCCACCGTTA CCGAACAAGC 60

TGGCGTGGTC GCCAGCACCC CCGGCACCGC CGACGCCGGA GTCGAACAAT GGCACCGTCG 120

TATCCCCACC ATTGCCGCCG GNCCCACCGG CACCG 155

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATGGCGTTCA CGGGGCGCCG GGGACCGGGC AGCCCGGNGG GGCCGGGGGG TGG 53

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 132 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GATCCACCGC GGGTGCAGAC GGTGCCCGCG GCGCCACCCC GACCAGCGGC GGCAACGGCG 60

GCACCGGCGG CAACGGCGCG AACGCCACCG TCGTCGGNGG GGCCGGCGGG GCCGGCGGCA 120

AGGGCGGCAA CG 132

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 132 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GATCGGCGGC CGGNACGGNC GGGGACGGCG GCAAGGGCGG NAACGGGGGC GCCGNAGCCA 60

CCNGCCAAGA ATCCTCCGNG TCCNCCAATG GCGCGAATGG CGGACAGGGC GGCAACGGCG 120

GCANCGGCGG CA 132

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 702 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CGGCACGAGG ATCGGTACCC CGCGGCATCG GCAGCTGCCG ATTCGCCGGG TTTCCCCACC 60

CGAGGAAAGC CGCTACCAGA TGGCGCTGCC GAAGTAGGGC GATCCGTTCG CGATGCCGGC 120

ATGAACGGGC GGCATCAAAT TAGTGCAGGA ACCTTTCAGT TTAGCGACGA TAATGGCTAT 180

AGCACTAAGG AGGATGATCC GATATGACGC AGTCGCAGAC CGTGACGGTG GATCAGCAAG 240

AGATTTTGAA CAGGGCCAAC GAGGTGGAGG CCCCGATGGC GGACCCACCG ACTGATGTCC 300

CCATCACACC GTGCGAACTC ACGGNGGNTA AAAACGCCGC CCAACAGNTG GTNTTGTCCG 360

CCGACAACAT GCGGGAATAC CTGGCGGCCG GTGCCAAAGA GCGGCAGCGT CTGGCGACCT 420

CGCTGCGCAA CGCGGCCAAG GNGTATGGCG AGGTTGATGA GGAGGCTGCG ACCGCGCTGG 480

ACAACGACGG CGAAGGAACT GTGCAGGCAG AATCGGCCGG GGCCGTCGGA GGGGACAGTT 540

CGGCCGAACT AACCGATACG CCGAGGGTGG CCACGGCCGG TGAACCCAAC TTCATGGATC 600

TCAAAGAAGC GGCAAGGAAG CTCGAAACGG GCGACCAAGG CGCATCGCTC GCGCACTGNG 660

GGGATGGGTG GAACACTTNC ACCCTGACGC TGCAAGGCGA CG 702

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 298 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAAGCCGCAG CGCTGTCGGG CGACGTGGCG GTCAAAGCGG CATCGCTCGG TGGCGGTGGA 60

GGCGGCGGGG TGCCGTCGGC GCCGTTGGGA TCCGCGATCG GGGGCGCCGA ATCGGTGCGG 120

CCCGCTGGCG CTGGTGACAT TGCCGGCTTA GGCCAGGGAA GGGCCGGCGG CGGCGCCGCG 180

CTGGGCGGCG GTGGCATGGG AATGCCGATG GGTGCCGCGC ATCAGGGACA AGGGGGCGCC 240

AAGTCCAAGG GTTCTCAGCA GGAAGACGAG GCGCTCTACA CCGAGGATCC TCGTGCCG 298

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1058 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGGCACGAGG ATCGAATCGC GTCGCCGGGA GCACAGCGTC GCACTGCACC AGTGGAGGAG 60

CCATGACCTA CTCGCCGGGT AACCCCGGAT ACCCGCAAGC GCAGCCCGCA GGCTCCTACG 120

GAGGCGTCAC ACCCTCGTTC GCCCACGCCG ATGAGGGTGC GAGCAAGCTA CCGATGTACC 180

TGAACATCGC GGTGGCAGTG CTCGGTCTGG CTGCGTACTT CGCCAGCTTC GGCCCAATGT 240

TCACCCTCAG TACCGAACTC GGGGGGGGTG ATGGCGCAGT GTCCGGTGAC ACTGGGCTGC 300

CGGTCGGGGT GGCTCTGCTG GCTGCGCTGC TTGCCGGGGT GGTTCTGGTG CCTAAGGCCA 360

AGAGCCATGT GACGGTAGTT GCGGTGCTCG GGGTACTCGG CGTATTTCTG ATGGTCTCGG 420

CGACGTTTAA CAAGCCCAGC GCCTATTCGA CCGGTTGGGC ATTGTGGGTT GTGTTGGCTT 480

TCATCGTGTT CCAGGCGGTT GCGGCAGTCC TGGCGCTCTT GGTGGAGACC GGCGCTATCA 540

CCGCGCCGGC GCCGCGGCCC AAGTTCGACC CGTATGGACA GTACGGGCGG TACGGGCAGT 600

ACGGGCAGTA CGGGGTGCAG CCGGGTGGGT ACTACGGTCA GCAGGGTGCT CAGCAGGCCG 660

CGGGACTGCA GTCGCCCGGC CCGCAGCAGT CTCCGCAGCC TCCCGGATAT GGGTCGCAGT 720

ACGGCGGCTA TTCGTCCAGT CCGAGCCAAT CGGGCAGTGG ATACACTGCT CAGCCCCCGG 780

CCCAGCCGCC GGCGCAGTCC GGGTCGCAAC AATCGCACCA GGGCCCATCC ACGCCACCTA 840

CCGGCTTTCC GAGCTTCAGC CCACCACCAC CGGTCAGTGC CGGGACGGGG TCGCAGGCTG 900

GTTCGGCTCC AGTCAACTAT TCAAACCCCA GCGGGGGCGA GCAGTCGTCG TCCCCCGGGG 960

GGGCGCCGGT CTAACCGGGC GTTCCCGCGT CCGGTCGCGC GTGTGCGCGA AGAGTGAACA 1020

GGGTGTCAGC AAGCGCGGAC GATCCTCGTG CCGAATTC 1058

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 327 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGGCACGAGA GACCGATGCC GCTACCCTCG CGCAGGAGGC AGGTAATTTC GAGCGGATCT 60

CCGGCGACCT GAAAACCCAG ATCGACCAGG TGGAGTCGAC GGCAGGTTCG TTGCAGGGCC 120

AGTGGCGCGG CGCGGCGGGG ACGGCCGCCC AGGCCGCGGT GGTGCGCTTC CAAGAAGCAG 180

CCAATAAGCA GAAGCAGGAA CTCGACGAGA TCTCGACGAA TATTCGTCAG GCCGGCGTCC 240

AATACTCGAG GGCCGACGAG GAGCAGCAGC AGGCGCTGTC CTCGCAAATG GGCTTCTGAC 300

CCGCTAATAC GAAAAGAAAC GGAGCAA 327

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGGTCGCGAT GATGGCGTTG TCGAACGTGA CCGATTCTGT ACCGCCGTCG TTGAGATCAA 60

CCAACAACGT GTTGGCGTCG GCAAATGTGC CGNACCCGTG GATCTCGGTG ATCTTGTTCT 120

TCTTCATCAG GAAGTGCACA CCGGCCACCC TGCCCTCGGN TACCTTTCGG 170

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 127 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GATCCGGCGG CACGGGGGGT GCCGGCGGCA GCACCGCTGG CGCTGGCGGC AACGGCGGGG 60

CCGGGGGTGG CGGCGGAACC GGTGGGTTGC TCTTCGGCAA CGGCGGTGCC GGCGGGCACG 120

GGGCCGT 127

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 81 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CGGCGGCAAG GGCGGCACCG CCGGCAACGG GAGCGGCGCG GCCGGCGGCA ACGGCGGCAA 60

CGGCGGCTCC GGCCTCAACG G 81

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 149 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GATCAGGGCT GGCCGGCTCC GGCCAGAAGG GCGGTAACGG AGGAGCTGCC GGATTGTTTG 60

GCAACGGCGG GGCCGGNGGT GCCGGCGCGT CCAACCAAGC CGGTAACGGC GGNGCCGGCG 120

GAAACGGTGG TGCCGGTGGG CTGATCTGG 149

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 355 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGGCACGAGA TCACACCTAC CGAGTGATCG AGATCGTCGG GACCTCGCCC GACGGTGTCG 60

ACGCGGNAAT CCAGGGCGGT CTGGCCCGAG CTGCGCAGAC CATGCGCGCG CTGGACTGGT 120

TCGAAGTACA GTCAATTCGA GGCCACCTGG TCGACGGAGC GGTCGCGCAC TTCCAGGTGA 180

CTATGAAAGT CGGCTTCCGC CTGGAGGATT CCTGAACCTT CAAGCGCGGC CGATAACTGA 240

GGTGCATCAT TAAGCGACTT TTCCAGAACA TCCTGACGCG CTCGAAACGC GGTTCAGCCG 300

ACGGTGGCTC CGCCGAGGCG CTGCCTCCAA AATCCCTGCG ACAATTCGTC GGCGG 355

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 999 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATGCATCACC ATCACCATCA CATGCATCAG GTGGACCCCA ACTTGACACG TCGCAAGGGA 60

CGATTGGCGG CACTGGCTAT CGCGGCGATG GCCAGCGCCA GCCTGGTGAC CGTTGCGGTG 120

CCCGCGACCG CCAACGCCGA TCCGGAGCCA GCGCCCCCGG TACCCACAAC GGCCGCCTCG 180

CCGCCGTCGA CCGCTGCAGC GCCACCCGCA CCGGCGACAC CTGTTGCCCC CCCACCACCG 240

GCCGCCGCCA ACACGCCGAA TGCCCAGCCG GGCGATCCCA ACGCAGCACC TCCGCCGGCC 300

GACCCGAACG CACCGCCGCC ACCTGTCATT GCCCCAAACG CACCCCAACC TGTCCGGATC 360

GACAACCCGG TTGGAGGATT CAGCTTCGCG CTGCCTGCTG GCTGGGTGGA GTCTGACGCC 420

GCCCACTTCG ACTACGGTTC AGCACTCCTC AGCAAAACCA CCGGGGACCC GCCATTTCCC 480

GGACAGCCGC CGCCGGTGGC CAATGACACC CGTATCGTGC TCGGCCGGCT AGACCAAAAG 540

CTTTACGCCA GCGCCGAAGC CACCGACTCC AAGGCCGCGG CCCGGTTGGG CTCGGACATG 600

GGTGAGTTCT ATATGCCCTA CCCGGGCACC CGGATCAACC AGGAAACCGT CTCGCTCGAC 660

GCCAACGGGG TGTCTGGAAG CGCGTCGTAT TACGAAGTCA AGTTCAGCGA TCCGAGTAAG 720

CCGAACGGCC AGATCTGGAC GGGCGTAATC GGCTCGCCCG CGGCGAACGC ACCGGACGCC 780

GGGCCCCCTC AGCGCTGGTT TGTGGTATGG CTCGGGACCG CCAACAACCC GGTGGACAAG 840

GGCGCGGCCA AGGCGCTGGC CGAATCGATC CGGCCTTTGG TCGCCCCGCC GCCGGCGCCG 900

GCACCGGCTC CTGCAGAGCC CGCTCCGGCG CCGGCGCCGG CCGGGGAAGT CGCTCCTACC 960

CCGACGACAC CGACACCGCA GCGGACCTTA CCGGCCTGA 999

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 332 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met His His His His His His Met His Gln Val Asp Pro Asn Leu Thr
1 5 10 15

Arg Arg Lys Gly Arg Leu Ala Ala Leu Ala Ile Ala Ala Met Ala Ser
20 25 30

Ala Ser Leu Val Thr Val Ala Val Pro Ala Thr Ala Asn Ala Asp Pro
35 40 45

Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro Ser Thr
50 55 60

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro
65 70 75 80

Ala Ala Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala
85 90 95

Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro
100 105 110

Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser
115 120 125

Phe Ala Leu Pro Ala Gly Trp Val Glu Ser Asp Ala Ala His Phe Asp
130 135 140

Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro
145 150 155 160

Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg
165 170 175

Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala
180 185 190

Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro
195 200 205

Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val
210 215 220

Ser Gly Ser Ala Ser Tyr Tyr Glu Val Lys Phe Ser Asp Pro Ser Lys
225 230 235 240

Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn
245 250 255

Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly
260 265 270

Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu
275 280 285

Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro
290 295 300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr
305 310 315 320

Pro Thr Thr Pro Thr Pro Gln Arg Thr Leu Pro Ala
325 330

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Xaa Asn Tyr Gly Gln Val
1 5 10 15

Val Ala Ala Leu
20

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala Ala Lys
1 5 10 15

Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp Pro Ala Trp Gly Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Asp Ile Gly Ser Glu Ser Thr Glu Asp Gln Gln Xaa Ala Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Ala Glu Glu Ser Ile Ser Thr Xaa Glu Xaa Ile Val Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Ala Ala Ala Ala Pro Pro
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Ala Pro Lys Thr Tyr Xaa Glu Glu Leu Lys Gly Thr Asp Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Gln Thr Ser
1 5 10 15

Leu Leu Asn Asn Leu Ala Asp Pro Asp Val Ser Phe Ala Asp
20 25 30

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Gly Cys Gly Asp Arg Ser Gly Gly Asn Leu Asp Gln Ile Arg Leu Arg
1 5 10 15

Arg Asp Arg Ser Gly Gly Asn Leu
20

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 187 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Thr Gly Ser Leu Asn Gln Thr His Asn Arg Arg Ala Asn Glu Arg Lys
1 5 10 15

Asn Thr Thr Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala
20 25 30

Ala Ala Ala Ile Gly Ala Ala Ala Ala Gly Val Thr Ser Ile Met Ala
35 40 45

Gly Gly Pro Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro
50 55 60

Leu Pro Leu Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln
65 70 75 80

Leu Thr Ser Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala
85 90 95

Asn Lys Gly Ser Leu Val Glu Gly Gly Ile Gly Gly Thr Glu Ala Arg
100 105 110

Ile Ala Asp His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro
115 120 125

Leu Ser Phe Ser Val Thr Asn Ile Gln Pro Ala Ala Ala Gly Ser Ala
130 135 140

Thr Ala Asp Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr
145 150 155 160

Gln Asn Val Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala
165 170 175

Ser Ala Met Glu Leu Leu Gln Ala Ala Gly Xaa
180 185

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 148 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Asp Glu Val Thr Val Glu Thr Thr Ser Val Phe Arg Ala Asp Phe Leu
1 5 10 15

Ser Glu Leu Asp Ala Pro Ala Gln Ala Gly Thr Glu Ser Ala Val Ser
20 25 30

Gly Val Glu Gly Leu Pro Pro Gly Ser Ala Leu Leu Val Val Lys Arg
35 40 45

Gly Pro Asn Ala Gly Ser Arg Phe Leu Leu Asp Gln Ala Ile Thr Ser
50 55 60

Ala Gly Arg His Pro Asp Ser Asp Ile Phe Leu Asp Asp Val Thr Val
65 70 75 80

Ser Arg Arg His Ala Glu Phe Arg Leu Glu Asn Asn Glu Phe Asn Val
85 90 95

Val Asp Val Gly Ser Leu Asn Gly Thr Tyr Val Asn Arg Glu Pro Val
100 105 110

Asp Ser Ala Val Leu Ala Asn Gly Asp Glu Val Gln Ile Gly Lys Leu
115 120 125

Arg Leu Val Phe Leu Thr Gly Pro Lys Gln Gly Glu Asp Asp Gly Ser
130 135 140

Thr Gly Gly Pro
145

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 230 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Thr Ser Asn Arg Pro Ala Arg Arg Gly Arg Arg Ala Pro Arg Asp Thr
1 5 10 15

Gly Pro Asp Arg Ser Ala Ser Leu Ser Leu Val Arg His Arg Arg Gln
20 25 30

Gln Arg Asp Ala Leu Cys Leu Ser Ser Thr Gln Ile Ser Arg Gln Ser
35 40 45

Asn Leu Pro Pro Ala Ala Gly Gly Ala Ala Asn Tyr Ser Arg Arg Asn
50 55 60

Phe Asp Val Arg Ile Lys Ile Phe Met Leu Val Thr Ala Val Val Leu
65 70 75 80

Leu Cys Cys Ser Gly Val Ala Thr Ala Ala Pro Lys Thr Tyr Cys Glu
85 90 95

Glu Leu Lys Gly Thr Asp Thr Gly Gln Ala Cys Gln Ile Gln Met Ser
100 105 110

Asp Pro Ala Tyr Asn Ile Asn Ile Ser Leu Pro Ser Tyr Tyr Pro Asp
115 120 125

Gln Lys Ser Leu Glu Asn Tyr Ile Ala Gln Thr Arg Asp Lys Phe Leu
130 135 140

Ser Ala Ala Thr Ser Ser Thr Pro Arg Glu Ala Pro Tyr Glu Leu Asn
145 150 155 160

Ile Thr Ser Ala Thr Tyr Gln Ser Ala Ile Pro Pro Arg Gly Thr Gln
165 170 175

Ala Val Val Leu Xaa Val Tyr His Asn Ala Gly Gly Thr His Pro Thr
180 185 190

Thr Thr Tyr Lys Ala Phe Asp Trp Asp Gln Ala Tyr Arg Lys Pro Ile
195 200 205

Thr Tyr Asp Thr Leu Trp Gln Ala Asp Thr Asp Pro Leu Pro Val Val
210 215 220

Phe Pro Ile Val Ala Arg
225 230

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 132 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1 5 10 15

Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
20 25 30

Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
35 40 45

Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
50 55 60

Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65 70 75 80

Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
85 90 95

Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
100 105 110

Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
115 120 125

Gly Pro Pro Ala
130

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 100 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Val Pro Leu Arg Ser Pro Ser Met Ser Pro Ser Lys Cys Leu Ala Ala
1 5 10 15

Ala Gln Arg Asn Pro Val Ile Arg Arg Arg Arg Leu Ser Asn Pro Pro
20 25 30

Pro Arg Lys Tyr Arg Ser Met Pro Ser Pro Ala Thr Ala Ser Ala Gly
35 40 45

Met Ala Arg Val Arg Arg Arg Ala Ile Trp Arg Gly Pro Ala Thr Xaa
50 55 60

Ser Ala Gly Met Ala Arg Val Arg Arg Trp Xaa Val Met Pro Xaa Val
65 70 75 80

Ile Gln Ser Thr Xaa Ile Arg Xaa Xaa Gly Pro Phe Asp Asn Arg Gly
85 90 95

Ser Glu Arg Lys
100

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 163 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Thr Asp Asp Ile Leu Leu Ile Asp Thr Asp Glu Arg Val Arg Thr
1 5 10 15

Leu Thr Leu Asn Arg Pro Gln Ser Arg Asn Ala Leu Ser Ala Ala Leu
20 25 30

Arg Asp Arg Phe Phe Ala Xaa Leu Xaa Asp Ala Glu Xaa Asp Asp Asp
35 40 45

Ile Asp Val Val Ile Leu Thr Gly Ala Asp Pro Val Phe Cys Ala Gly
50 55 60

Leu Asp Leu Lys Val Ala Gly Arg Ala Asp Arg Ala Ala Gly His Leu
65 70 75 80

Thr Ala Val Gly Gly His Asp Gln Ala Gly Asp Arg Arg Asp Gln Arg
85 90 95

Arg Arg Gly His Arg Arg Ala Arg Thr Gly Ala Val Leu Arg His Pro
100 105 110

Asp Arg Leu Arg Ala Arg Pro Leu Arg Arg His Pro Arg Pro Gly Gly
115 120 125

Ala Ala Ala His Leu Gly Thr Gln Cys Val Leu Ala Ala Lys Gly Arg
130 135 140

His Arg Xaa Gly Pro Val Asp Glu Pro Asp Arg Arg Leu Pro Val Arg
145 150 155 160

Asp Arg Arg

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 344 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Met Lys Phe Val Asn His Ile Glu Pro Val Ala Pro Arg Arg Ala Gly
1 5 10 15

Gly Ala Val Ala Glu Val Tyr Ala Glu Ala Arg Arg Glu Phe Gly Arg
20 25 30

Leu Pro Glu Pro Leu Ala Met Leu Ser Pro Asp Glu Gly Leu Leu Thr
35 40 45

Ala Gly Trp Ala Thr Leu Arg Glu Thr Leu Leu Val Gly Gln Val Pro
50 55 60

Arg Gly Arg Lys Glu Ala Val Ala Ala Ala Val Ala Ala Ser Leu Arg
65 70 75 80

Cys Pro Trp Cys Val Asp Ala His Thr Thr Met Leu Tyr Ala Ala Gly
85 90 95

Gln Thr Asp Thr Ala Ala Ala Ile Leu Ala Gly Thr Ala Pro Ala Ala
100 105 110

Gly Asp Pro Asn Ala Pro Tyr Val Ala Trp Ala Ala Gly Thr Gly Thr
115 120 125

Pro Ala Gly Pro Pro Ala Pro Phe Gly Pro Asp Val Ala Ala Glu Tyr
130 135 140

Leu Gly Thr Ala Val Gln Phe His Phe Ile Ala Arg Leu Val Leu Val
145 150 155 160

Leu Leu Asp Glu Thr Phe Leu Pro Gly Gly Pro Arg Ala Gln Gln Leu
165 170 175

Met Arg Arg Ala Gly Gly Leu Val Phe Ala Arg Lys Val Arg Ala Glu
180 185 190

His Arg Pro Gly Arg Ser Thr Arg Arg Leu Glu Pro Arg Thr Leu Pro
195 200 205

Asp Asp Leu Ala Trp Ala Thr Pro Ser Glu Pro Ile Ala Thr Ala Phe
210 215 220

Ala Ala Leu Ser His His Leu Asp Thr Ala Pro His Leu Pro Pro Pro
225 230 235 240

Thr Arg Gln Val Val Arg Arg Val Val Gly Ser Trp His Gly Glu Pro
245 250 255

Met Pro Met Ser Ser Arg Trp Thr Asn Glu His Thr Ala Glu Leu Pro
260 265 270

Ala Asp Leu His Ala Pro Thr Arg Leu Ala Leu Leu Thr Gly Leu Ala
275 280 285

Pro His Gln Val Thr Asp Asp Asp Val Ala Ala Ala Arg Ser Leu Leu
290 295 300

Asp Thr Asp Ala Ala Leu Val Gly Ala Leu Ala Trp Ala Ala Phe Thr
305 310 315 320

Ala Ala Arg Arg Ile Gly Thr Trp Ile Gly Ala Ala Ala Glu Gly Gln
325 330 335

Val Ser Arg Gln Asn Pro Thr Gly
340

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 485 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Asp Asp Pro Asp Met Pro Gly Thr Val Ala Lys Ala Val Ala Asp Ala
1 5 10 15

Leu Gly Arg Gly Ile Ala Pro Val Glu Asp Ile Gln Asp Cys Val Glu
20 25 30

Ala Arg Leu Gly Glu Ala Gly Leu Asp Asp Val Ala Arg Val Tyr Ile
35 40 45

Ile Tyr Arg Gln Arg Arg Ala Glu Leu Arg Thr Ala Lys Ala Leu Leu
50 55 60

Gly Val Arg Asp Glu Leu Lys Leu Ser Leu Ala Ala Val Thr Val Leu
65 70 75 80

Arg Glu Arg Tyr Leu Leu His Asp Glu Gln Gly Arg Pro Ala Glu Ser
85 90 95

Thr Gly Glu Leu Met Asp Arg Ser Ala Arg Cys Val Ala Ala Ala Glu
100 105 110

Asp Gln Tyr Glu Pro Gly Ser Ser Arg Arg Trp Ala Glu Arg Phe Ala
115 120 125

Thr Leu Leu Arg Asn Leu Glu Phe Leu Pro Asn Ser Pro Thr Leu Met
130 135 140

Asn Ser Gly Thr Asp Leu Gly Leu Leu Ala Gly Cys Phe Val Leu Pro
145 150 155 160

Ile Glu Asp Ser Leu Gln Ser Ile Phe Ala Thr Leu Gly Gln Ala Ala
165 170 175

Glu Leu G Arg Ala Gly Gly Gly Thr Gly Tyr Ala Phe Ser His Leu
180 185 190

Arg Pro Ala Gly Asp Arg Val Ala Ser Thr Gly Gly Thr Ala Ser Gly
195 200 205

Pro Val Ser Phe Leu Arg Leu Tyr Asp Ser Ala Ala Gly Val Val Ser
210 215 220

Met Gly Gly Arg Arg Arg Gly Ala Cys Met Ala Val Leu Asp Val Ser
225 230 235 240

His Pro Asp Ile Cys Asp Phe Val Thr Ala Lys Ala Glu Ser Pro Ser
245 250 255

Glu Leu Pro His Phe Asn Leu Ser Val Gly Val Thr Asp Ala Phe Leu
260 265 270

Arg Ala Val Glu Arg Asn Gly Leu His Arg Leu Val Asn Pro Arg Thr
275 280 285

Gly Lys Ile Val Ala Arg Met Pro Ala Ala Glu Leu Phe Asp Ala Ile
290 295 300

Cys Lys Ala Ala His Ala Gly Gly Asp Pro Gly Leu Val Phe Leu Asp
305 310 315 320

Thr Ile Asn Arg Ala Asn Pro Val Pro Gly Arg Gly Arg Ile Glu Ala
325 330 335

Thr Asn Pro Cys Gly Glu Val Pro Leu Leu Pro Tyr Glu Ser Cys Asn
340 345 350

Leu Gly Ser Ile Asn Leu Ala Arg Met Leu Ala Asp Gly Arg Val Asp
355 360 365

Trp Asp Arg Leu Glu Glu Val Ala Gly Val Ala Val Arg Phe Leu Asp
370 375 380

Asp Val Ile Asp Val Ser Arg Tyr Pro Phe Pro Glu Leu Gly Glu Ala
385 390 395 400

Ala Arg Ala Thr Arg Lys Ile Gly Leu Gly Val Met Gly Leu Ala Glu
405 410 415

Leu Leu Ala Ala Leu Gly Ile Pro Tyr Asp Ser Glu Glu Ala Val Arg
420 425 430

Leu Ala Thr Arg Leu Met Arg Arg Ile Gln Gln Ala Ala His Thr Ala
435 440 445

Ser Arg Arg Leu Ala Glu Glu Arg Gly Ala Phe Pro Ala Phe Thr Asp
450 455 460

Ser Arg Phe Ala Arg Ser Gly Pro Arg Arg Asn Ala Gln Val Thr Ser
465 470 475 480

Val Ala Pro Thr Gly
485

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 267 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Gly Val Ile Val Leu Asp Leu Glu Pro Arg Gly Pro Leu Pro Thr Glu
1 5 10 15

Ile Tyr Trp Arg Arg Arg Gly Leu Ala Leu Gly Ile Ala Val Val Val
20 25 30

Val Gly Ile Ala Val Ala Ile Val Ile Ala Phe Val Asp Ser Ser Ala
35 40 45

Gly Ala Lys Pro Val Ser Ala Asp Lys Pro Ala Ser Ala Gln Ser His
50 55 60

Pro Gly Ser Pro Ala Pro Gln Ala Pro Gln Pro Ala Gly Gln Thr Glu
65 70 75 80

Gly Asn Ala Ala Ala Ala Pro Pro Gln Gly Gln Asn Pro Glu Thr Pro
85 90 95

Thr Pro Thr Ala Ala Val Gln Pro Pro Pro Val Leu Lys Glu Gly Asp
100 105 110

Asp Cys Pro Asp Ser Thr Leu Ala Val Lys Gly Leu Thr Asn Ala Pro
115 120 125

Gln Tyr Tyr Val Gly Asp Gln Pro Lys Phe Thr Met Val Val Thr Asn
130 135 140

Ile Gly Leu Val Ser Cys Lys Arg Asp Val Gly Ala Ala Val Leu Ala
145 150 155 160

Ala Tyr Val Tyr Ser Leu Asp Asn Lys Arg Leu Trp Ser Asn Leu Asp
165 170 175

Cys Ala Pro Ser Asn Glu Thr Leu Val Lys Thr Phe Ser Pro Gly Glu
180 185 190

Gln Val Thr Thr Ala Val Thr Trp Thr Gly Met Gly Ser Ala Pro Arg
195 200 205

Cys Pro Leu Pro Arg Pro Ala Ile Gly Pro Gly Thr Tyr Asn Leu Val
210 215 220

Val Gln Leu Gly Asn Leu Arg Ser Leu Pro Val Pro Phe Ile Leu Asn
225 230 235 240

Gln Pro Pro Pro Pro Pro Gly Pro Val Pro Ala Pro Gly Pro Ala Gln
245 250 255

Ala Pro Pro Pro Glu Ser Pro Ala Gln Gly Gly
260 265

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly Val Gln Val
1 5 10 15

Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu Val Val Ala
20 25 30

Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val Val Val Thr
35 40 45

Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu Val Ala Ala
50 55 60

Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr Phe Gln Asp
65 70 75 80

Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly Lys Ala Glu
85 90 95

Gln

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 364 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Gly Ala Ala Val Ser Leu Leu Ala Ala Gly Thr Leu Val Leu Thr Ala
1 5 10 15

Cys Gly Gly Gly Thr Asn Ser Ser Ser Ser Gly Ala Gly Gly Thr Ser
20 25 30

Gly Ser Val His Cys Gly Gly Lys Lys Glu Leu His Ser Ser Gly Ser
35 40 45

Thr Ala Gln Glu Asn Ala Met Glu Gln Phe Val Tyr Ala Tyr Val Arg
50 55 60

Ser Cys Pro Gly Tyr Thr Leu Asp Tyr Asn Ala Asn Gly Ser Gly Ala
65 70 75 80

Gly Val Thr Gln Phe Leu Asn Asn Glu Thr Asp Phe Ala Gly Ser Asp
85 90 95

Val Pro Leu Asn Pro Ser Thr Gly Gln Pro Asp Arg Ser Ala Glu Arg
100 105 110

Cys Gly Ser Pro Ala Trp Asp Leu Pro Thr Val Phe Gly Pro Ile Ala
115 120 125

Ile Thr Tyr Asn Ile Lys Gly Val Ser Thr Leu Asn Leu Asp Gly Pro
130 135 140

Thr Thr Ala Lys Ile Phe Asn Gly Thr Ile Thr Val Trp Asn Asp Pro
145 150 155 160

Gln Ile Gln Ala Leu Asn Ser Gly Thr Asp Leu Pro Pro Thr Pro Ile
165 170 175

Ser Val Ile Phe Arg Ser Asp Lys Ser Gly Thr Ser Asp Asn Phe Gln
180 185 190

Lys Tyr Leu Asp Gly Val Ser Asn Gly Ala Trp Gly Lys Gly Ala Ser
195 200 205

Glu Thr Phe Ser Gly Gly Val Gly Val Gly Ala Ser Gly Asn Asn Gly
210 215 220

Thr Ser Ala Leu Leu Gln Thr Thr Asp Gly Ser Ile Thr Tyr Asn Glu
225 230 235 240

Trp Ser Phe Ala Val Gly Lys Gln Leu Asn Met Ala Gln Ile Ile Thr
245 250 255

Ser Ala Gly Pro Asp Pro Val Ala Ile Thr Thr Glu Ser Val Gly Lys
260 265 270

Thr Ile Ala Gly Ala Lys Ile Met Gly Gln Gly Asn Asp Leu Val Leu
275 280 285

Asp Thr Ser Ser Phe Tyr Arg Pro Thr Gln Pro Gly Ser Tyr Pro Ile
290 295 300

Val Leu Ala Thr Tyr Glu Ile Val Cys Ser Lys Tyr Pro Asp Ala Thr
305 310 315 320

Thr Gly Thr Ala Val Arg Ala Phe Met Gln Ala Ala Ile Gly Pro Gly
325 330 335

Gln Glu Gly Leu Asp Gln Tyr Gly Ser Ile Pro Leu Pro Lys Ser Phe
340 345 350

Gln Ala Lys Leu Ala Ala Ala Val Asn Ala Ile Ser
355 360

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 309 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Gln Ala Ala Ala Gly Arg Ala Val Arg Arg Thr Gly His Ala Glu Asp
1 5 10 15

Gln Thr His Gln Asp Arg Leu His His Gly Cys Arg Arg Ala Ala Val
20 25 30

Val Val Arg Gln Asp Arg Ala Ser Val Ser Ala Thr Ser Ala Arg Pro
35 40 45

Pro Arg Arg His Pro Ala Gln Gly His Arg Arg Arg Val Ala Pro Ser
50 55 60

Gly Gly Arg Arg Arg Pro His Pro His His Val Gln Pro Asp Asp Arg
65 70 75 80

Arg Asp Arg Pro Ala Leu Leu Asp Arg Thr Gln Pro Ala Glu His Pro
85 90 95

Asp Pro His Arg Arg Gly Pro Ala Asp Pro Gly Arg Val Arg Gly Arg
100 105 110

Gly Arg Leu Arg Arg Val Asp Asp Gly Arg Leu Gln Pro Asp Arg Asp
115 120 125

Ala Asp His Gly Ala Pro Val Arg Gly Arg Gly Pro His Arg Gly Val
130 135 140

Gln His Arg Gly Gly Pro Val Phe Val Arg Arg Val Pro Gly Val Arg
145 150 155 160

Cys Ala His Arg Arg Gly His Arg Arg Val Ala Ala Pro Gly Gln Gly
165 170 175

Asp Val Leu Arg Ala Gly Leu Arg Val Glu Arg Leu Arg Pro Val Ala
180 185 190

Ala Val Glu Asn Leu His Arg Gly Ser Gln Arg Ala Asp Gly Arg Val
195 200 205

Phe Arg Pro Ile Arg Arg Gly Ala Arg Leu Pro Ala Arg Arg Ser Arg
210 215 220

Ala Gly Pro Gln Gly Arg Leu His Leu Asp Gly Ala Gly Pro Ser Pro
225 230 235 240

Leu Pro Ala Arg Ala Gly Gln Gln Gln Pro Ser Ser Ala Gly Gly Arg
245 250 255

Arg Ala Gly Gly Ala Glu Arg Ala Asp Pro Gly Gln Arg Gly Arg His
260 265 270

His Gln Gly Gly His Asp Pro Gly Arg Gln Gly Ala Gln Arg Gly Thr
275 280 285

Ala Gly Val Ala His Ala Ala Ala Gly Pro Arg Arg Ala Ala Val Arg
290 295 300

Asn Arg Pro Arg Arg
305

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 580 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Ser Ala Val Trp Cys Leu Asn Gly Phe Thr Gly Arg His Arg His Gly
1 5 10 15

Arg Cys Arg Val Arg Ala Ser Gly Trp Arg Ser Ser Asn Arg Trp Cys
20 25 30

Ser Thr Thr Ala Asp Cys Cys Ala Ser Lys Thr Pro Thr Gln Ala Ala
35 40 45

Ser Pro Leu Glu Arg Arg Phe Thr Cys Cys Ser Pro Ala Val Gly Cys
50 55 60

Arg Phe Arg Ser Phe Pro Val Arg Arg Leu Ala Leu Gly Ala Arg Thr
65 70 75 80

Ser Arg Thr Leu Gly Val Arg Arg Thr Leu Ser Gln Trp Asn Leu Ser
85 90 95

Pro Arg Ala Gln Pro Ser Cys Ala Val Thr Val Glu Ser His Thr His
100 105 110

Ala Ser Pro Arg Met Ala Lys Leu Ala Arg Val Val Gly Leu Val Gln
115 120 125

Glu Glu Gln Pro Ser Asp Met Thr Asn His Pro Arg Tyr Ser Pro Pro
130 135 140

Pro Gln Gln Pro Gly Thr Pro Gly Tyr Ala Gln Gly Gln Gln Gln Thr
145 150 155 160

Tyr Ser Gln Gln Phe Asp Trp Arg Tyr Pro Pro Ser Pro Pro Pro Gln
165 170 175

Pro Thr Gln Tyr Arg Gln Pro Tyr Glu Ala Leu Gly Gly Thr Arg Pro
180 185 190

Gly Leu Ile Pro Gly Val Ile Pro Thr Met Thr Pro Pro Pro Gly Met
195 200 205

Val Arg Gln Arg Pro Arg Ala Gly Met Leu Ala Ile Gly Ala Val Thr
210 215 220

Ile Ala Val Val Ser Ala Gly Ile Gly Gly Ala Ala Ala Ser Leu Val
225 230 235 240

Gly Phe Asn Arg Ala Pro Ala Gly Pro Ser Gly Gly Pro Val Ala Ala
245 250 255

Ser Ala Ala Pro Ser Ile Pro Ala Ala Asn Met Pro Pro Gly Ser Val
260 265 270

Glu Gln Val Ala Ala Lys Val Val Pro Ser Val Val Met Leu Glu Thr
275 280 285

Asp Leu Gly Arg Gln Ser Glu Glu Gly Ser Gly Ile Ile Leu Ser Ala
290 295 300

Glu Gly Leu Ile Leu Thr Asn Asn His Val Ile Ala Ala Ala Ala Lys
305 310 315 320

Pro Pro Leu Gly Ser Pro Pro Pro Lys Thr Thr Val Thr Phe Ser Asp
325 330 335

Gly Arg Thr Ala Pro Phe Thr Val Val Gly Ala Asp Pro Thr Ser Asp
340 345 350

Ile Ala Val Val Arg Val Gln Gly Val Ser Gly Leu Thr Pro Ile Ser
355 360 365

Leu Gly Ser Ser Ser Asp Leu Arg Val Gly Gln Pro Val Leu Ala Ile
370 375 380

Gly Ser Pro Leu Gly Leu Glu Gly Thr Val Thr Thr Gly Ile Val Ser
385 390 395 400

Ala Leu Asn Arg Pro Val Ser Thr Thr Gly Glu Ala Gly Asn Gln Asn
405 410 415

Thr Val Leu Asp Ala Ile Gln Thr Asp Ala Ala Ile Asn Pro Gly Asn
420 425 430

Ser Gly Gly Ala Leu Val Asn Met Asn Ala Gln Leu Val Gly Val Asn
435 440 445

Ser Ala Ile Ala Thr Leu Gly Ala Asp Ser Ala Asp Ala Gln Ser Gly
450 455 460

Ser Ile Gly Leu Gly Phe Ala Ile Pro Val Asp Gln Ala Lys Arg Ile
465 470 475 480

Ala Asp Glu Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly
485 490 495

Val Gln Val Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu
500 505 510

Val Val Ala Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val
515 520 525

Val Val Thr Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu
530 535 540

Val Ala Ala Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr
545 550 555 560

Phe Gln Asp Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly
565 570 575

Lys Ala Glu Gln
580

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 233 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Met Asn Asp Gly Lys Arg Ala Val Thr Ser Ala Val Leu Val Val Leu
1 5 10 15

Gly Ala Cys Leu Ala Leu Trp Leu Ser Gly Cys Ser Ser Pro Lys Pro
20 25 30

Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr Ala Ser Asp Pro
35 40 45

Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala Thr Lys Gly Leu
50 55 60

Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys Val Asp Ser Leu
65 70 75 80

Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala Asn Pro Leu Ala
85 90 95

Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly Val Pro Phe Arg
100 105 110

Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp Asp Trp Ser Asn
115 120 125

Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val Leu Asp Pro Ala
130 135 140

Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn Leu Gln Ala Gln
145 150 155 160

Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys Ile Thr Gly Thr
165 170 175

Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly Ala Lys Ser Ala
180 185 190

Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser His His Leu Val
195 200 205

Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln Leu Thr Gln Ser
210 215 220

Lys Trp Asn Glu Pro Val Asn Val Asp
225 230

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 66 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Val Ile Asp Ile Ile Gly Thr Ser Pro Thr Ser Trp Glu Gln Ala Ala
1 5 10 15

Ala Glu Ala Val Gln Arg Ala Arg Asp Ser Val Asp Asp Ile Arg Val
20 25 30

Ala Arg Val Ile Glu Gln Asp Met Ala Val Asp Ser Ala Gly Lys Ile
35 40 45

Thr Tyr Arg Ile Lys Leu Glu Val Ser Phe Lys Met Arg Pro Ala Gln
50 55 60

Pro Arg
65

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 69 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Val Pro Pro Ala Pro Pro Leu Pro Pro Leu Pro Pro Ser Pro Ile Ser
1 5 10 15

Cys Ala Ser Pro Pro Ser Pro Pro Leu Pro Pro Ala Pro Pro Val Ala
20 25 30

Pro Gly Pro Pro Met Pro Pro Leu Asp Pro Trp Pro Pro Ala Pro Pro
35 40 45

Leu Pro Tyr Ser Thr Pro Pro Gly Ala Pro Leu Pro Pro Ser Pro Pro
50 55 60

Ser Pro Pro Leu Pro
65

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 355 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Met Ser Asn Ser Arg Arg Arg Ser Leu Arg Trp Ser Trp Leu Leu Ser
1 5 10 15

Val Leu Ala Ala Val Gly Leu Gly Leu Ala Thr Ala Pro Ala Gln Ala
20 25 30

Ala Pro Pro Ala Leu Ser Gln Asp Arg Phe Ala Asp Phe Pro Ala Leu
35 40 45

Pro Leu Asp Pro Ser Ala Met Val Ala Gln Val Ala Pro Gln Val Val
50 55 60

Asn Ile Asn Thr Lys Leu Gly Tyr Asn Asn Ala Val Gly Ala Gly Thr
65 70 75 80

Gly Ile Val Ile Asp Pro Asn Gly Val Val Leu Thr Asn Asn His Val
85 90 95

Ile Ala Gly Ala Thr Asp Ile Asn Ala Phe Ser Val Gly Ser Gly Gln
100 105 110

Thr Tyr Gly Val Asp Val Val Gly Tyr Asp Arg Thr Gln Asp Val Ala
115 120 125

Val Leu Gln Leu Arg Gly Ala Gly Gly Leu Pro Ser Ala Ala Ile Gly
130 135 140

Gly Gly Val Ala Val Gly Glu Pro Val Val Ala Met Gly Asn Ser Gly
145 150 155 160

Gly Gln Gly Gly Thr Pro Arg Ala Val Pro Gly Arg Val Val Ala Leu
165 170 175

Gly Gln Thr Val Gln Ala Ser Asp Ser Leu Thr Gly Ala Glu Glu Thr
180 185 190

Leu Asn Gly Leu Ile Gln Phe Asp Ala Ala Ile Gln Pro Gly Asp Ser
195 200 205

Gly Gly Pro Val Val Asn Gly Leu Gly Gln Val Val Gly Met Asn Thr
210 215 220

Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe Ala
225 230 235 240

Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser Gly
245 250 255

Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly Leu
260 265 270

Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val Val
275 280 285

Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val Ile
290 295 300

Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala Asp
305 310 315 320

Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp Gln
325 330 335

Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu Gly
340 345 350

Pro Pro Ala
355

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 205 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
Ser Pro Lys Pro Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr
1               5                  10                  15

Ala Ser Asp Pro Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala
            20                  25                  30

Thr Lys Gly Leu Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys
        35                  40                  45

Val Asp Ser Leu Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala
    50                  55                  60

Asn Pro Leu Ala Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly
65                  70                  75                  80

Val Pro Phe Arg Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp
                85                  90                  95

Asp Trp Ser Asn Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val
            100                 105                 110

Leu Asp Pro Ala Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn
        115                 120                 125

Leu Gln Ala Gln Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys
    130                 135                 140

Ile Thr Gly Thr Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly
145                 150                 155                 160

Ala Lys Ser Ala Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser
                165                 170                 175

His His Leu Val Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln
            180                 185                 190
```

Leu Thr Gln Ser Lys Trp Asn Glu Pro Val Asn Val Asp
195 200 205

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 286 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Gly Asp Ser Phe Trp Ala Ala Ala Asp Gln Met Ala Arg Gly Phe Val
1 5 10 15

Leu Gly Ala Thr Ala Gly Arg Thr Thr Leu Thr Gly Glu Gly Leu Gln
20 25 30

His Ala Asp Gly His Ser Leu Leu Leu Asp Ala Thr Asn Pro Ala Val
35 40 45

Val Ala Tyr Asp Pro Ala Phe Ala Tyr Glu Ile Gly Tyr Ile Xaa Glu
50 55 60

Ser Gly Leu Ala Arg Met Cys Gly Glu Asn Pro Glu Asn Ile Phe Phe
65 70 75 80

Tyr Ile Thr Val Tyr Asn Glu Pro Tyr Val Gln Pro Pro Glu Pro Glu
85 90 95

Asn Phe Asp Pro Glu Gly Val Leu Gly Gly Ile Tyr Arg Tyr His Ala
100 105 110

Ala Thr Glu Gln Arg Thr Asn Lys Xaa Gln Ile Leu Ala Ser Gly Val
115 120 125

Ala Met Pro Ala Ala Leu Arg Ala Ala Gln Met Leu Ala Ala Glu Trp
130 135 140

Asp Val Ala Ala Asp Val Trp Ser Val Thr Ser Trp Gly Glu Leu Asn
145 150 155 160

Arg Asp Gly Val Val Ile Glu Thr Glu Lys Leu Arg His Pro Asp Arg
165 170 175

Pro Ala Gly Val Pro Tyr Val Thr Arg Ala Leu Glu Asn Ala Arg Gly
180 185 190

Pro Val Ile Ala Val Ser Asp Trp Met Arg Ala Val Pro Glu Gln Ile
195 200 205

Arg Pro Trp Val Pro Gly Thr Tyr Leu Thr Leu Gly Thr Asp Gly Phe
210 215 220

Gly Phe Ser Asp Thr Arg Pro Ala Gly Arg Arg Tyr Phe Asn Thr Asp
225 230 235 240

Ala Glu Ser Gln Val Gly Arg Gly Phe Gly Arg Gly Trp Pro Gly Arg
245 250 255

Arg Val Asn Ile Asp Pro Phe Gly Ala Gly Arg Gly Pro Pro Ala Gln
260 265 270

Leu Pro Gly Phe Asp Glu Gly Gly Gly Leu Arg Pro Xaa Lys
275 280 285

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 173 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Thr Lys Phe His Ala Leu Met Gln Glu Gln Ile His Asn Glu Phe Thr
1 5 10 15

Ala Ala Gln Gln Tyr Val Ala Ile Ala Val Tyr Phe Asp Ser Glu Asp
20 25 30

Leu Pro Gln Leu Ala Lys His Phe Tyr Ser Gln Ala Val Glu Glu Arg
35 40 45

Asn His Ala Met Met Leu Val Gln His Leu Leu Asp Arg Asp Leu Arg
50 55 60

Val Glu Ile Pro Gly Val Asp Thr Val Arg Asn Gln Phe Asp Arg Pro
65 70 75 80

Arg Glu Ala Leu Ala Leu Ala Leu Asp Gln Glu Arg Thr Val Thr Asp
85 90 95

Gln Val Gly Arg Leu Thr Ala Val Ala Arg Asp Glu Gly Asp Phe Leu
100 105 110

Gly Glu Gln Phe Met Gln Trp Phe Leu Gln Glu Gln Ile Glu Glu Val
115 120 125

Ala Leu Met Ala Thr Leu Val Arg Val Ala Asp Arg Ala Gly Ala Asn
130 135 140

Leu Phe Glu Leu Glu Asn Phe Val Ala Arg Glu Val Asp Val Ala Pro
145 150 155 160

Ala Ala Ser Gly Ala Pro His Ala Ala Gly Gly Arg Leu
165 170

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Arg Ala Asp Glu Arg Lys Asn Thr Thr Met Lys Met Val Lys Ser Ile
1 5 10 15

Ala Ala Gly Leu Thr Ala Ala Ala Ala Ile Gly Ala Ala Ala Ala Gly
20 25 30

Val Thr Ser Ile Met Ala Gly Gly Pro Val Val Tyr Gln Met Gln Pro
35 40 45

Val Val Phe Gly Ala Pro Leu Pro Leu Asp Pro Xaa Ser Ala Pro Xaa
50 55 60

Val Pro Thr Ala Ala Gln Trp Thr Xaa Leu Leu Asn Xaa Leu Xaa Asp
65 70 75 80

Pro Asn Val Ser Phe Xaa Asn Lys Gly Ser Leu Val Glu Gly Gly Ile
85 90 95

Gly Gly Xaa Glu Gly Xaa Xaa Arg Arg Xaa Gln
100 105

(2) INFORMATION FOR SEQ ID NO:85:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 125 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Val Leu Ser Val Pro Val Gly Asp Gly Phe Trp Xaa Arg Val Val Asn
1 5 10 15

Pro Leu Gly Gln Pro Ile Asp Gly Arg Gly Asp Val Asp Ser Asp Thr
20 25 30

Arg Arg Ala Leu Glu Leu Gln Ala Pro Ser Val Val Xaa Arg Gln Gly
35 40 45

Val Lys Glu Pro Leu Xaa Thr Gly Ile Lys Ala Ile Asp Ala Met Thr
50 55 60

Pro Ile Gly Arg Gly Gln Arg Gln Leu Ile Ile Gly Asp Arg Lys Thr
65 70 75 80

Gly Lys Asn Arg Arg Leu Cys Arg Thr Pro Ser Ser Asn Gln Arg Glu
85 90 95

Glu Leu Gly Val Arg Trp Ile Pro Arg Ser Arg Cys Ala Cys Val Tyr
100 105 110

Val Gly His Arg Ala Arg Arg Gly Thr Tyr His Arg Arg
115 120 125

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Cys Asp Ala Val Met Gly Phe Leu Gly Gly Ala Gly Pro Leu Ala Val
1 5 10 15

Val Asp Gln Gln Leu Val Thr Arg Val Pro Gln Gly Trp Ser Phe Ala
20 25 30

Gln Ala Ala Ala Val Pro Val Val Phe Leu Thr Ala Trp Tyr Gly Leu
35 40 45

Ala Asp Leu Ala Glu Ile Lys Ala Gly Glu Ser Val Leu Ile His Ala
50 55 60

Gly Thr Gly Gly Val Gly Met Ala Ala Val Gln Leu Ala Arg Gln Trp
65 70 75 80

Gly Val Glu Val Phe Val Thr Ala Ser Arg Gly Lys Trp Asp Thr Leu
85 90 95

Arg Ala Xaa Xaa Phe Asp Asp Xaa Pro Tyr Arg Xaa Phe Pro His Xaa
100 105 110

Arg Ser Ser Xaa Gly
115

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 103 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Met Tyr Arg Phe Ala Cys Arg Thr Leu Met Leu Ala Ala Cys Ile Leu
1 5 10 15

Ala Thr Gly Val Ala Gly Leu Gly Val Gly Ala Gln Ser Ala Ala Gln
20 25 30

Thr Ala Pro Val Pro Asp Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp
35 40 45

Pro Ala Trp Gly Pro Asn Trp Asp Pro Tyr Thr Cys His Asp Asp Phe
50 55 60

His Arg Asp Ser Asp Gly Pro Asp His Ser Arg Asp Tyr Pro Gly Pro
65 70 75 80

Ile Leu Glu Gly Pro Val Leu Asp Asp Pro Gly Ala Ala Pro Pro Pro
85 90 95

Pro Ala Ala Gly Gly Gly Ala
100

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Val Gln Cys Arg Val Trp Leu Glu Ile Gln Trp Arg Gly Met Leu Gly
1 5 10 15

Ala Asp Gln Ala Arg Ala Gly Gly Pro Ala Arg Ile Trp Arg Glu His
20 25 30

Ser Met Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala
35 40 45

Thr Lys Glu Gly Arg Gly Ile Val Met Arg Val Pro Leu Glu Gly Gly
50 55 60

Gly Arg Leu Val Val Glu Leu Thr Pro Asp Glu Ala Ala Ala Leu Gly
65 70 75 80

Asp Glu Leu Lys Gly Val Thr Ser
85

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 95 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn Phe Glu Arg Ile
1 5 10 15

Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala Gly
20 25 30

Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln Ala
35 40 45

Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu Leu
50 55 60

Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg
65 70 75 80

Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
85 90 95

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 166 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Met Thr Gln Ser Gln Thr Val Thr Val Asp Gln Gln Glu Ile Leu Asn
1 5 10 15

Arg Ala Asn Glu Val Glu Ala Pro Met Ala Asp Pro Pro Thr Asp Val
20 25 30

Pro Ile Thr Pro Cys Glu Leu Thr Xaa Xaa Lys Asn Ala Ala Gln Gln
35 40 45

Xaa Val Leu Ser Ala Asp Asn Met Arg Glu Tyr Leu Ala Ala Gly Ala
50 55 60

Lys Glu Arg Gln Arg Leu Ala Thr Ser Leu Arg Asn Ala Ala Lys Xaa
65 70 75 80

Tyr Gly Glu Val Asp Glu Glu Ala Ala Thr Ala Leu Asp Asn Asp Gly
85 90 95

Glu Gly Thr Val Gln Ala Glu Ser Ala Gly Ala Val Gly Gly Asp Ser
100 105 110

Ser Ala Glu Leu Thr Asp Thr Pro Arg Val Ala Thr Ala Gly Glu Pro
115 120 125

Asn Phe Met Asp Leu Lys Glu Ala Ala Arg Lys Leu Glu Thr Gly Asp
130 135 140

Gln Gly Ala Ser Leu Ala His Xaa Gly Asp Gly Trp Asn Thr Xaa Thr
145 150 155 160

Leu Thr Leu Gln Gly Asp
165

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Arg Ala Glu Arg Met
1 5

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 263 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Val Ala Trp Met Ser Val Thr Ala Gly Gln Ala Glu Leu Thr Ala Ala
1 5 10 15

Gln Val Arg Val Ala Ala Ala Ala Tyr Glu Thr Ala Tyr Gly Leu Thr
20 25 30

Val Pro Pro Pro Val Ile Ala Glu Asn Arg Ala Glu Leu Met Ile Leu
35 40 45

Ile Ala Thr Asn Leu Leu Gly Gln Asn Thr Pro Ala Ile Ala Val Asn
50 55 60

Glu Ala Glu Tyr Gly Glu Met Trp Ala Gln Asp Ala Ala Ala Met Phe
65 70 75 80

Gly Tyr Ala Ala Ala Thr Ala Thr Ala Thr Ala Thr Leu Leu Pro Phe
85 90 95

Glu Glu Ala Pro Glu Met Thr Ser Ala Gly Gly Leu Leu Glu Gln Ala
100 105 110

Ala Ala Val Glu Glu Ala Ser Asp Thr Ala Ala Ala Asn Gln Leu Met
115 120 125

Asn Asn Val Pro Gln Ala Leu Lys Gln Leu Ala Gln Pro Thr Gln Gly
130 135 140

Thr Thr Pro Ser Ser Lys Leu Gly Gly Leu Trp Lys Thr Val Ser Pro
145 150 155 160

His Arg Ser Pro Ile Ser Asn Met Val Ser Met Ala Asn Asn His Met
165 170 175

Ser Met Thr Asn Ser Gly Val Ser Met Thr Asn Thr Leu Ser Ser Met
180 185 190

Leu Lys Gly Phe Ala Pro Ala Ala Ala Ala Gln Ala Val Gln Thr Ala
195 200 205

Ala Gln Asn Gly Val Arg Ala Met Ser Ser Leu Gly Ser Ser Leu Gly
210 215 220

Ser Ser Gly Leu Gly Gly Gly Val Ala Ala Asn Leu Gly Arg Ala Ala
225 230 235 240

Ser Val Arg Tyr Gly His Arg Asp Gly Gly Lys Tyr Ala Xaa Ser Gly
245 250 255

Arg Arg Asn Gly Gly Pro Ala
260

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 303 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Met Thr Tyr Ser Pro Gly Asn Pro Gly Tyr Pro Gln Ala Gln Pro Ala
1 5 10 15

Gly Ser Tyr Gly Gly Val Thr Pro Ser Phe Ala His Ala Asp Glu Gly
20 25 30

Ala Ser Lys Leu Pro Met Tyr Leu Asn Ile Ala Val Ala Val Leu Gly
35 40 45

Leu Ala Ala Tyr Phe Ala Ser Phe Gly Pro Met Phe Thr Leu Ser Thr
50 55 60

Glu Leu Gly Gly Gly Asp Gly Ala Val Ser Gly Asp Thr Gly Leu Pro
65 70 75 80

Val Gly Val Ala Leu Leu Ala Ala Leu Leu Ala Gly Val Val Leu Val
85 90 95

Pro Lys Ala Lys Ser His Val Thr Val Val Ala Val Leu Gly Val Leu
100 105 110

Gly Val Phe Leu Met Val Ser Ala Thr Phe Asn Lys Pro Ser Ala Tyr
115 120 125

Ser Thr Gly Trp Ala Leu Trp Val Val Leu Ala Phe Ile Val Phe Gln
130 135 140

Ala Val Ala Ala Val Leu Ala Leu Leu Val Glu Thr Gly Ala Ile Thr
145 150 155 160

Ala Pro Ala Pro Arg Pro Lys Phe Asp Pro Tyr Gly Gln Tyr Gly Arg
165 170 175

Tyr Gly Gln Tyr Gly Gln Tyr Gly Val Gln Pro Gly Gly Tyr Tyr Gly
180 185 190

Gln Gln Gly Ala Gln Gln Ala Ala Gly Leu Gln Ser Pro Gly Pro Gln
195 200 205

Gln Ser Pro Gln Pro Pro Gly Tyr Gly Ser Gln Tyr Gly Gly Tyr Ser
210 215 220

Ser Ser Pro Ser Gln Ser Gly Ser Gly Tyr Thr Ala Gln Pro Pro Ala
225 230 235 240

Gln Pro Pro Ala Gln Ser Gly Ser Gln Gln Ser His Gln Gly Pro Ser
245 250 255

Thr Pro Pro Thr Gly Phe Pro Ser Phe Ser Pro Pro Pro Pro Val Ser
260 265 270

Ala Gly Thr Gly Ser Gln Ala Gly Ser Ala Pro Val Asn Tyr Ser Asn
275 280 285

Pro Ser Gly Gly Glu Gln Ser Ser Ser Pro Gly Gly Ala Pro Val
290 295 300

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 168 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala Ala Ala Ala
1 5 10 15

Ile Gly Ala Ala Ala Ala Gly Val Thr Ser Ile Met Ala Gly Gly Pro
20 25 30

Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro Leu Pro Leu
35 40 45

Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser
50 55 60

Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn Lys Gly
65 70 75 80

Ser Leu Val Glu Gly Gly Ile Gly Gly Thr Glu Ala Arg Ile Ala Asp
85 90 95

His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro Leu Ser Phe
100 105 110

Ser Val Thr Asn Ile Gln Pro Ala Ala Ala Gly Ser Ala Thr Ala Asp
115 120 125

Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr Gln Asn Val
130 135 140

Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala Ser Ala Met
145 150 155 160

Glu Leu Leu Gln Ala Ala Gly Asn
165

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 332 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Met His His His His His His Met His Gln Val Asp Pro Asn Leu Thr
1 5 10 15

Arg Arg Lys Gly Arg Leu Ala Ala Leu Ala Ile Ala Ala Met Ala Ser
20 25 30

Ala Ser Leu Val Thr Val Ala Val Pro Ala Thr Ala Asn Ala Asp Pro
35 40 45

Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro Ser Thr
50 55 60

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro
65 70 75 80

Ala Ala Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala
85 90 95

Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro
100 105 110

Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser
115 120 125

Phe Ala Leu Pro Ala Gly Trp Val Glu Ser Asp Ala Ala His Phe Asp
130 135 140

Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro
145 150 155 160

Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg
165 170 175

Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala
180 185 190

Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro
195 200 205

Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val
210 215 220

Ser Gly Ser Ala Ser Tyr Tyr Glu Val Lys Phe Ser Asp Pro Ser Lys
225 230 235 240

Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn
245 250 255

Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly
260 265 270

Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu
275 280 285

Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro
290 295 300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr
305 310 315 320

Pro Thr Thr Pro Thr Pro Gln Arg Thr Leu Pro Ala
325 330

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 500 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CGTGGCAATG TCGTTGACCG TCGGGGCCGG GGTCGCCTCC GCAGATCCCG TGGACGCGGT 60

CATTAACACC ACCTGCAATT ACGGGCAGGT AGTAGCTGCG CTCAACGCGA CGGATCCGGG 120

GGCTGCCGCA CAGTTCAACG CCTCACCGGT GGCGCAGTCC TATTTGCGCA ATTTCCTCGC 180

CGCACCGCCA CCTCAGCGCG CTGCCATGGC CGCGCAATTG CAAGCTGTGC CGGGGGCGGC 240

ACAGTACATC GGCCTTGTCG AGTCGGTTGC CGGCTCCTGC AACAACTATT AAGCCCATGC 300

GGGCCCCATC CCGCGACCCG GCATCGTCGC CGGGGCTAGG CCAGATTGCC CCGCTCCTCA 360

ACGGGCCGCA TCCCGCGACC CGGCATCGTC GCCGGGGCTA GGCCAGATTG CCCCGCTCCT 420

CAACGGGCCG CATCTCGTGC CGAATTCCTG CAGCCCGGGG GATCCACTAG TTCTAGAGCG 480

GCCGCCACCG CGGTGGAGCT 500

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 96 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Val Ala Met Ser Leu Thr Val Gly Ala Gly Val Ala Ser Ala Asp Pro
1 5 10 15

Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val Val Ala
20 25 30

Ala Leu Asn Ala Thr Asp Pro Gly Ala Ala Ala Gln Phe Asn Ala Ser
35 40 45

Pro Val Ala Gln Ser Tyr Leu Arg Asn Phe Leu Ala Ala Pro Pro Pro
50 55 60

Gln Arg Ala Ala Met Ala Ala Gln Leu Gln Ala Val Pro Gly Ala Ala
65 70 75 80

Gln Tyr Ile Gly Leu Val Glu Ser Val Ala Gly Ser Cys Asn Asn Tyr
85 90 95

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 154 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

ATGACAGAGC AGCAGTGGAA TTTCGCGGGT ATCGAGGCCG CGGCAAGCGC AATCCAGGGA 60

AATGTCACGT CCATTCATTC CCTCCTTGAC GAGGGGAAGC AGTCCCTGAC CAAGCTCGCA 120

GCGGCCTGGG GCGGTAGCGG TTCGGAAGCG TACC 154

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Met Thr Glu Gln Gln Trp Asn Phe Ala Gly Ile Glu Ala Ala Ala Ser
1 5 10 15

Ala Ile Gln Gly Asn Val Thr Ser Ile His Ser Leu Leu Asp Glu Gly
20 25 30

Lys Gln Ser Leu Thr Lys Leu Ala Ala Ala Trp Gly Gly Ser Gly Ser
35 40 45

Glu Ala Tyr
50

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 282 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

CGGTCGCGCA CTTCCAGGTG ACTATGAAAG TCGGCTTCCG NCTGGAGGAT TCCTGAACCT 60

TCAAGCGCGG CCGATAACTG AGGTGCATCA TTAAGCGACT TTTCCAGAAC ATCCTGACGC 120

GCTCGAAACG CGGCACAGCC GACGGTGGCT CCGNCGAGGC GCTGNCTCCA AAATCCCTGA 180

GACAATTCGN CGGGGGCGCC TACAAGGAAG TCGGTGCTGA ATTCGNCGNG TATCTGGTCG 240

ACCTGTGTGG TCTGNAGCCG GACGAAGCGG TGCTCGACGT CG 282

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1565 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

GTATGCGGCC ACTGAAGTCG CCAATGCGGC GGCGGCCAGC TAAGCCAGGA ACAGTCGGCA 60

CGAGAAACCA CGAGAAATAG GGACACGTAA TGGTGGATTT CGGGGCGTTA CCACCGGAGA 120

TCAACTCCGC GAGGATGTAC GCCGGCCCGG GTTCGGCCTC GCTGGTGGCC GCGGCTCAGA 180

TGTGGGACAG CGTGGCGAGT GACCTGTTTT CGGCCGCGTC GGCGTTTCAG TCGGTGGTCT 240

GGGGTCTGAC GGTGGGGTCG TGGATAGGTT CGTCGGCGGG TCTGATGGTG GCGGCGGCCT 300

CGCCGTATGT GGCGTGGATG AGCGTCACCG CGGGGCAGGC CGAGCTGACC GCCGCCCAGG 360

TCCGGGTTGC TGCGGCGGCC TACGAGACGG CGTATGGGCT GACGGTGCCC CCGCCGGTGA 420

TCGCCGAGAA CCGTGCTGAA CTGATGATTC TGATAGCGAC CAACCTCTTG GGGCAAAACA 480

CCCCGGCGAT CGCGGTCAAC GAGGCCGAAT ACGGCGAGAT GTGGGCCCAA GACGCCGCCG 540

CGATGTTTGG CTACGCCGCG GCGACGGCGA CGGCGACGGC GACGTTGCTG CCGTTCGAGG 600

AGGCGCCGGA GATGACCAGC GCGGGTGGGC TCCTCGAGCA GGCCGCCGCG GTCGAGGAGG 660

CCTCCGACAC CGCCGCGGCG AACCAGTTGA TGAACAATGT GCCCCAGGCG CTGCAACAGC 720

TGGCCCAGCC CACGCAGGGC ACCACGCCTT CTTCCAAGCT GGGTGGCCTG TGGAAGACGG 780

TCTCGCCGCA TCGGTCGCCG ATCAGCAACA TGGTGTCAAT GGCCAACAAC CACATGTCAA 840

TGACCAACTC GGGTGTGTCA ATGACCAACA CCTTGAGCTC GATGTTGAAG GGCTTTGCTC 900

CGGCGGCGGC CGCCCAGGCC GTGCAAACCG CGGCGCAAAA CGGGGTCCGG GCGATGAGCT 960

CGCTGGGCAG CTCGCTGGGT TCTTCGGGTC TGGGCGGTGG GGTGGCCGCC AACTTGGGTC 1020

GGGCGGCCTC GGTCGGTTCG TTGTCGGTGC CGCAGGCCTG GGCCGCGGCC AACCAGGCAG 1080

TCACCCCGGC GGCGCGGGCG CTGCCGCTGA CCAGCCTGAC CAGCGCCGCG GAAAGAGGGC 1140

CCGGGCAGAT GCTGGGCGGG CTGCCGGTGG GGCAGATGGG CGCCAGGGCC GGTGGTGGGC 1200

TCAGTGGTGT GCTGCGTGTT CCGCCGCGAC CCTATGTGAT GCCGCATTCT CCGGCGGCCG 1260

GCTAGGAGAG GGGGCGCAGA CTGTCGTTAT TTGACCAGTG ATCGGCGGTC TCGGTGTTTC 1320

CGCGGCCGGC TATGACAACA GTCAATGTGC ATGACAAGTT ACAGGTATTA GGTCCAGGTT 1380

CAACAAGGAG ACAGGCAACA TGGCCTCACG TTTTATGACG GATCCGCACG CGATGCGGGA 1440

CATGGCGGGC CGTTTTGAAG TGCACGCCCA GACGGTGGAG GACGAGGCTC GCCGGATGTG 1500

GGCGTCCGCG CAAAACATTT CCGGTGCGGG CTGGAGTGGC ATGGCCGAGG CGACCTCGCT 1560

AGACA 1565

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 391 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Met Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met
1 5 10 15

Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Gln Met Trp
20 25 30

Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser
35 40 45

Val Val Trp Gly Leu Thr Val Gly Ser Trp Ile Gly Ser Ser Ala Gly
50 55 60

Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr
65 70 75 80

Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala
85 90 95

Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala
100 105 110

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly
115 120 125

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met
130 135 140

Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Ala Thr Ala
145 150 155 160

Thr Ala Thr Ala Thr Leu Leu Pro Phe Glu Glu Ala Pro Glu Met Thr
165 170 175

Ser Ala Gly Gly Leu Leu Glu Gln Ala Ala Ala Val Glu Glu Ala Ser
180 185 190

Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu
195 200 205

Gln Gln Leu Ala Gln Pro Thr Gln Gly Thr Thr Pro Ser Ser Lys Leu
210 215 220

Gly Gly Leu Trp Lys Thr Val Ser Pro His Arg Ser Pro Ile Ser Asn
225 230 235 240

Met Val Ser Met Ala Asn Asn His Met Ser Met Thr Asn Ser Gly Val
245 250 255

Ser Met Thr Asn Thr Leu Ser Ser Met Leu Lys Gly Phe Ala Pro Ala
260 265 270

Ala Ala Ala Gln Ala Val Gln Thr Ala Ala Gln Asn Gly Val Arg Ala
275 280 285

Met Ser Ser Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Gly Gly
290 295 300

Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser Val
305 310 315 320

Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala Arg
325 330 335

Ala Leu Pro Leu Thr Ser Leu Thr Ser Ala Ala Glu Arg Gly Pro Gly
340 345 350

Gln Met Leu Gly Gly Leu Pro Val Gly Gln Met Gly Ala Arg Ala Gly
355 360 365

Gly Gly Leu Ser Gly Val Leu Arg Val Pro Pro Arg Pro Tyr Val Met
370 375 380

Pro His Ser Pro Ala Ala Gly
385 390

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

ACCAACACCT TGCACTCNAT GTTGAAGGGC TTAGCTCCGG CGGCGGCTCA GGCCGTGGAA 60

ACCGCGGCGG AAAACGGGGT CTGGGCAATG AGCTCGCTGG GCAGCCAGCT GGGTTCGTCG 120

CTGGGTTCTT CGGGTCTGGG CGCTGGGGTG GCCGCCAACT TGGGTCGGGC GGCCTCGGTC 180

GGTTCGTTGT CGGTGCCGCC AGCATGGGCC GCGGCCAACC AGGCGGTCAC CCCGGCGGCG 240

CGGGCGCTGC CGCTGACCA 259

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Thr Asn Thr Leu His Ser Met Leu Lys Gly Leu Ala Pro Ala Ala Ala
1 5 10 15

Gln Ala Val Glu Thr Ala Ala Glu Asn Gly Val Trp Ala Met Ser Ser
20 25 30

Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Ala
35 40 45

Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser
50 55 60

Val Pro Pro Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala
65 70 75 80

Arg Ala Leu Pro Leu Thr
85

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1109 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

TACTTGAGAG AATTTGACCT GTTGCCGACG TTGTTTGCTG TCCATCATTG GTGCTAGTTA 60

TGGCCGAGCG GAAGGATTAT CGAAGTGGTG GACTTCGGGG CGTTACCACC GGAGATCAAC 120

TCCGCGAGGA TGTACGCCGG CCCGGGTTCG GCCTCGCTGG TGGCCGCCGC GAAGATGTGG 180

GACAGCGTGG CGAGTGACCT GTTTTCGGCC GCGTCGGCGT TTCAGTCGGT GGTCTGGGGT 240

CTGACGACGG GATCGTGGAT AGGTTCGTCG GCGGGTCTGA TGGTGGCGGC GGCCTCGCCG 300

TATGTGGCGT GGATGAGCGT CACCGCGGGG CAGGCCGAGC TGACCGCCGC CCAGGTCCGG 360

GTTGCTGCGG CGGCCTACGA GACGGCGTAT GGGCTGACGG TGCCCCCGCC GGTGATCGCC 420

GAGAACCGTG CTGAACTGAT GATTCTGATA GCGACCAACC TCTTGGGGCA AAACACCCCG 480

GCGATCGCGG TCAACGAGGC CGAATACGGG GAGATGTGGG CCCAAGACGC CGCCGCGATG 540

TTTGGCTACG CCGCCACGGC GGCGACGGCG ACCGAGGCGT TGCTGCCGTT CGAGGACGCC 600

CCACTGATCA CCAACCCCGG CGGGCTCCTT GAGCAGGCCG TCGCGGTCGA GGAGGCCATC 660

GACACCGCCG CGGCGAACCA GTTGATGAAC AATGTGCCCC AAGCGCTGCA ACAACTGGCC 720

CAGCCCACGA AAAGCATCTG GCCGTTCGAC CAACTGAGTG AACTCTGGAA AGCCATCTCG 780

CCGCATCTGT CGCCGCTCAG CAACATCGTG TCGATGCTCA ACAACCACGT GTCGATGACC 840

AACTCGGGTG TGTCAATGGC CAGCACCTTG CACTCAATGT TGAAGGGCTT TGCTCCGGCG 900

GCGGCTCAGG CCGTGGAAAC CGCGGCGCAA AACGGGGTCC AGGCGATGAG CTCGCTGGGC 960

AGCCAGCTGG GTTCGTCGCT GGGTTCTTCG GGTCTGGGCG CTGGGGTGGC CGCCAACTTG 1020

GGTCGGGCGG CCTCGGTCGG TTCGTTGTCG GTGCCGCAGG CCTGGGCCGC GGCCAACCAG 1080

GCGGTCACCC CGGCGGCGCG GGCGCTGCC 1109

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 341 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Val Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met
1 5 10 15

Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Lys Met Trp
20 25 30

Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser
35 40 45

Val Val Trp Gly Leu Thr Thr Gly Ser Trp Ile Gly Ser Ser Ala Gly
50 55 60

Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr
65 70 75 80

Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala
85 90 95

Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala
100 105 110

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly
115 120 125

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met
130 135 140

Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Thr Ala Ala
145 150 155 160

Thr Ala Thr Glu Ala Leu Leu Pro Phe Glu Asp Ala Pro Leu Ile Thr
165 170 175

Asn Pro Gly Gly Leu Leu Glu Gln Ala Val Ala Val Glu Glu Ala Ile
180 185 190

Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu
195 200 205

Gln Gln Leu Ala Gln Pro Thr Lys Ser Ile Trp Pro Phe Asp Gln Leu
210 215 220

Ser Glu Leu Trp Lys Ala Ile Ser Pro His Leu Ser Pro Leu Ser Asn
225 230 235 240

Ile Val Ser Met Leu Asn Asn His Val Ser Met Thr Asn Ser Gly Val
245 250 255

Ser Met Ala Ser Thr Leu His Ser Met Leu Lys Gly Phe Ala Pro Ala
260 265 270

Ala Ala Gln Ala Val Glu Thr Ala Ala Gln Asn Gly Val Gln Ala Met
275 280 285

Ser Ser Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu
290 295 300

Gly Ala Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser
305 310 315 320

Leu Ser Val Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro
325 330 335

Ala Ala Arg Ala Leu
340

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1256 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

CATCGGAGGG AGTGATCACC ATGCTGTGGC ACGCAATGCC ACCGGAGNTA AATACCGCAC 60

GGCTGATGGC CGGCGCGGGT CCGGCTCCAA TGCTTGCGGC GGCCGCGGGA TGGCAGACGC 120

TTTCGGCGGC TCTGGACGCT CAGGCCGTCG AGTTGACCGC GCGCCTGAAC TCTCTGGGAG 180

AAGCCTGGAC TGGAGGTGGC AGCGACAAGG CGCTTGCGGC TGCAACGCCG ATGGTGGTCT 240

GGCTACAAAC CGCGTCAACA CAGGCCAAGA CCCGTGCGAT GCAGGCGACG GCGCAAGCCG 300

CGGCATACAC CCAGGCCATG GCCACGACGC CGTCGCTGCC GGAGATCGCC GCCAACCACA 360

TCACCCAGGC CGTCCTTACG GCCACCAACT TCTTCGGTAT CAACACGATC CCGATCGCGT 420

TGACCGAGAT GGATTATTTC ATCCGTATGT GGAACCAGGC AGCCCTGGCA ATGGAGGTCT 480

ACCAGGCCGA GACCGCGGTT AACACGCTTT TCGAGAAGCT CGAGCCGATG GCGTCGATCC 540

TTGATCCCGG CGCGAGCCAG AGCACGACGA ACCCGATCTT CGGAATGCCC TCCCCTGGCA 600

GCTCAACACC GGTTGGCCAG TTGCCGCCGG CGGCTACCCA GACCCTCGGC CAACTGGGTG 660

AGATGAGCGG CCCGATGCAG CAGCTGACCC AGCCGCTGCA GCAGGTGACG TCGTTGTTCA 720

GCCAGGTGGG CGGCACCGGC GGCGGCAACC CAGCCGACGA GGAAGCCGCG CAGATGGGCC 780

TGCTCGGCAC CAGTCCGCTG TCGAACCATC CGCTGGCTGG TGGATCAGGC CCCAGCGCGG 840

GCGCGGGCCT GCTGCGCGCG GAGTCGCTAC CTGGCGCAGG TGGGTCGTTG ACCCGCACGC 900

CGCTGATGTC TCAGCTGATC GAAAAGCCGG TTGCCCCCTC GGTGATGCCG GCGGCTGCTG 960

CCGGATCGTC GGCGACGGGT GGCGCCGCTC CGGTGGGTGC GGGAGCGATG GGCCAGGGTG 1020

CGCAATCCGG CGGCTCCACC AGGCCGGGTC TGGTCGCGCC GGCACCGCTC GCGCAGGAGC 1080

GTGAAGAAGA CGACGAGGAC GACTGGGACG AAGAGGACGA CTGGTGAGCT CCCGTAATGA 1140

CAACAGACTT CCCGGCCACC CGGGCCGGAA GACTTGCCAA CATTTTGGCG AGGAAGGTAA 1200

AGAGAGAAAG TAGTCCAGCA TGGCAGAGAT GAAGACCGAT GCCGCTACCC TCGCGC 1256

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 432 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

CTAGTGGATG GGACCATGGC CATTTTCTGC AGTCTCACTG CCTTCTGTGT TGACATTTTG 60

GCACGCCGGC GGAAACGAAG CACTGGGGTC GAAGAACGGC TGCGCTGCCA TATCGTCCGG 120

AGCTTCCATA CCTTCGTGCG GCCGGAAGAG CTTGTCGTAG TCGGCCGCCA TGACAACCTC 180

TCAGAGTGCG CTCAAACGTA TAAACACGAG AAAGGGCGAG ACCGACGGAA GGTCGAACTC 240

GCCCGATCCC GTGTTTCGCT ATTCTACGCG AACTCGGCGT TGCCCTATGC GAACATCCCA 300

GTGACGTTGC CTTCGGTCGA AGCCATTGCC TGACCGGCTT CGCTGATCGT CCGCGCCAGG 360

TTCTGCAGCG CGTTGTTCAG CTCGGTAGCC GTGGCGTCCC ATTTTTGCTG GACACCCTGG 420

TACGCCTCCG AA 432

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 368 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Met Leu Trp His Ala Met Pro Pro Glu Xaa Asn Thr Ala Arg Leu Met
1 5 10 15

Ala Gly Ala Gly Pro Ala Pro Met Leu Ala Ala Ala Ala Gly Trp Gln
20 25 30

Thr Leu Ser Ala Ala Leu Asp Ala Gln Ala Val Glu Leu Thr Ala Arg
35 40 45

Leu Asn Ser Leu Gly Glu Ala Trp Thr Gly Gly Gly Ser Asp Lys Ala
50 55 60

Leu Ala Ala Ala Thr Pro Met Val Val Trp Leu Gln Thr Ala Ser Thr
65 70 75 80

Gln Ala Lys Thr Arg Ala Met Gln Ala Thr Ala Gln Ala Ala Ala Tyr
85 90 95

Thr Gln Ala Met Ala Thr Thr Pro Ser Leu Pro Glu Ile Ala Ala Asn
100 105 110

His Ile Thr Gln Ala Val Leu Thr Ala Thr Asn Phe Phe Gly Ile Asn
115 120 125

Thr Ile Pro Ile Ala Leu Thr Glu Met Asp Tyr Phe Ile Arg Met Trp
130 135 140

Asn Gln Ala Ala Leu Ala Met Glu Val Tyr Gln Ala Glu Thr Ala Val
145 150 155 160

Asn Thr Leu Phe Glu Lys Leu Glu Pro Met Ala Ser Ile Leu Asp Pro
165 170 175

Gly Ala Ser Gln Ser Thr Thr Asn Pro Ile Phe Gly Met Pro Ser Pro
180 185 190

Gly Ser Ser Thr Pro Val Gly Gln Leu Pro Pro Ala Ala Thr Gln Thr
195 200 205

Leu Gly Gln Leu Gly Glu Met Ser Gly Pro Met Gln Gln Leu Thr Gln
210 215 220

Pro Leu Gln Gln Val Thr Ser Leu Phe Ser Gln Val Gly Gly Thr Gly
225 230 235 240

Gly Gly Asn Pro Ala Asp Glu Glu Ala Ala Gln Met Gly Leu Leu Gly
245 250 255

Thr Ser Pro Leu Ser Asn His Pro Leu Ala Gly Gly Ser Gly Pro Ser
260 265 270

Ala Gly Ala Gly Leu Leu Arg Ala Glu Ser Leu Pro Gly Ala Gly Gly
275 280 285

Ser Leu Thr Arg Thr Pro Leu Met Ser Gln Leu Ile Glu Lys Pro Val
290 295 300

Ala Pro Ser Val Met Pro Ala Ala Ala Ala Gly Ser Ser Ala Thr Gly
305 310 315 320

Gly Ala Ala Pro Val Gly Ala Gly Ala Met Gly Gln Gly Ala Gln Ser
325 330 335

Gly Gly Ser Thr Arg Pro Gly Leu Val Ala Pro Ala Pro Leu Ala Gln
340 345 350

Glu Arg Glu Glu Asp Asp Glu Asp Asp Trp Asp Glu Glu Asp Asp Trp
355 360 365

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Met Ala Glu Met Lys Thr Asp Ala Ala Thr Leu Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 396 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

GATCTCCGGC GACCTGAAAA CCCAGATCGA CCAGGTGGAG TCGACGGCAG GTTCGTTGCA 60

GGGCCAGTGG CGCGGCGCGG CGGGGACGGC CGCCCAGGCC GCGGTGGTGC GCTTCCAAGA 120

AGCAGCCAAT AAGCAGAAGC AGGAACTCGA CGAGATCTCG ACGAATATTC GTCAGGCCGG 180

CGTCCAATAC TCGAGGGCCG ACGAGGAGCA GCAGCAGGCG CTGTCCTCGC AAATGGGCTT 240

CTGACCCGCT AATACGAAAA GAAACGGAGC AAAAACATGA CAGAGCAGCA GTGGAATTTC 300

GCGGGTATCG AGGCCGCGGC AAGCGCAATC CAGGGAAATG TCACGTCCAT TCATTCCCTC 360

CTTGACGAGG GGAAGCAGTC CCTGACCAAG CTCGCA 396

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 80 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Ile Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala
1 5 10 15

Gly Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln
20 25 30

Ala Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu
35 40 45

Leu Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser
50 55 60

Arg Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
65 70 75 80

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 387 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

GTGGATCCCG ATCCCGTGTT TCGCTATTCT ACGCGAACTC GGCGTTGCCC TATGCGAACA 60

TCCCAGTGAC GTTGCCTTCG GTCGAAGCCA TTGCCTGACC GGCTTCGCTG ATCGTCCGCG 120

CCAGGTTCTG CAGCGCGTTG TTCAGCTCGG TAGCCGTGGC GTCCCATTTT TGCTGGACAC 180

CCTGGTACGC CTCCGAACCG CTACCGCCCC AGGCCGCTGC GAGCTTGGTC AGGGACTGCT 240

TCCCCTCGTC AAGGAGGGAA TGAATGGACG TGACATTTCC CTGGATTGCG CTTGCCGCGG 300

CCTCGATACC CGCGAAATTC CACTGCTGCT CTGTCATGTT TTTGCTCCGT TTCTTTTCGT 360

ATTAGCGGGT CAGAAGCCCA TTTGCGA 387

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 272 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

CGGCACGAGG ATCTCGGTTG GCCCAACGGC GCTGGCGAGG GCTCCGTTCC GGGGGCGAGC 60

TGCGCGCCGG ATGCTTCCTC TGCCCGCAGC CGCGCCTGGA TGGATGGACC AGTTGCTACC 120

TTCCCGACGT TTCGTTCGGT GTCTGTGCGA TAGCGGTGAC CCCGGCGCGC ACGTCGGGAG 180

TGTTGGGGGG CAGGCCGGGT CGGTGGTTCG GCCGGGGACG CAGACGGTCT GGACGGAACG 240

GGCGGGGGTT CGCCGATTGG CATCTTTGCC CA 272

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val
1 5 10 15

Val Ala Ala Leu
20

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala Ala Lys
1 5 10 15

Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp Pro Ala Trp Gly Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Asp Ile Gly Ser Glu Ser Thr Glu Asp Gln Gln Xaa Ala Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Ala Glu Glu Ser Ile Ser Thr Xaa Glu Xaa Ile Val Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro
1 5 10 15

Ser

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Ala Pro Lys Thr Tyr Xaa Glu Glu Leu Lys Gly Thr Asp Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser
1 5 10 15

Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn
20 25 30

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Asp Pro Pro Asp Pro His Gln Xaa Asp Met Thr Lys Gly Tyr Tyr Pro
1 5 10 15

Gly Gly Arg Arg Xaa Phe
20

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Asp Pro Gly Tyr Thr Pro Gly
1 5

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Second Residue Can Be Either a Pro or Thr"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Xaa Xaa Gly Phe Thr Gly Pro Gln Phe Tyr
1 5 10

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: /note= "The Third Residue Can Be Either a Gln or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Xaa Pro Xaa Val Thr Ala Tyr Ala Gly
1 5

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Xaa Xaa Xaa Glu Lys Pro Phe Leu Arg
1 5

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Xaa Asp Ser Glu Lys Ser Ala Thr Ile Lys Val Thr Asp Ala Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Ala Gly Asp Thr Xaa Ile Tyr Ile Val Gly Asn Leu Thr Ala Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Ala Pro Glu Ser Gly Ala Gly Leu Gly Gly Thr Val Gln Ala Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Xaa Tyr Ile Ala Tyr Xaa Thr Thr Ala Gly Ile Val Pro Gly Lys Ile
1 5 10 15

Asn Val His Leu Val
20

Claims

1. A polypeptide comprising an antigenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

(a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 115);

(b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 116);

(c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 17);

(d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro (SEQ ID No. 118);

(e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val (SEQ ID No. 119);

(f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 120);

(g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser (SEQ ID No. 121);

(h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 122);

(i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn (SEQ ID No. 123); and

(j) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131)

wherein Xaa may be any amino acid.

2. A polypeptide comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

(a) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 124) and

(b) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132), wherein Xaa may be any amino acid.

3. A polypeptide comprising an antigenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96 or a complement thereof under moderately stringent conditions.

4. A polypeptide comprising an antigenic portion of a *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos. 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 26-51 or a complement thereof under moderately stringent conditions.

5. A DNA molecule comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1-4.

6. A recombinant expression vector comprising a DNA molecule according to claim 5.

7. A host cell transformed with an expression vector according to claim 6.

8. The host cell of claim 7 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cells.

9. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting a biological sample with one or more polypeptides according to any of claims 1-4; and

(b) detecting in the sample the presence of antibodies that bind to at least one of the polypeptides, thereby detecting *M. tuberculosis* infection in the biological sample.

10. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting a biological sample with a polypeptide having an N-terminal sequence selected from the group consisting of sequences provided in SEQ ID No: 129 and 130; and

(b) detecting in the sample the presence of antibodies that bind to at least one of the polypeptides, thereby detecting *M. tuberculosis* infection in the biological sample.

11. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting a biological sample with one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 3, 11 and 12; and

(b) detecting in the sample the presence of antibodies that bind to at least one of the polypeptides, thereby detecting *M. tuberculosis* infection in the biological sample.

12. The method of any one of claims 9-11 wherein step (a) additionally comprises contacting the biological sample with a 38 kD *M. tuberculosis* antigen and step (b) additionally comprises detecting in the sample the presence of antibodies that bind to the 38 kD *M. tuberculosis* antigen.

13. The method of any one of claims 9-11 wherein the polypeptide(s) are bound to a solid support.

14. The method of claim 13 wherein the solid support comprises nitrocellulose, latex or a plastic material.

15. The method of any one of claims 9-11 wherein the biological sample is selected from the group consisting of whole blood, serum, plasma, saliva, cerebrospinal fluid and urine.

16. The method of claim 15 wherein the biological sample is whole blood or serum.

17. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, the first and the second oligonucleotide primers comprising at least about 10 contiguous nucleotides of a DNA molecule according to claim 5; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers, thereby detecting *M. tuberculosis* infection.

18. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, the first and the second oligonucleotide primers comprising at

least about 10 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers, thereby detecting *M. tuberculosis* infection.

19. The method of claims 17 or 18 wherein the biological sample is selected from the group consisting of whole blood, sputum, serum, plasma, saliva, cerebrospinal fluid and urine.

20. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the sample with one or more oligonucleotide probes comprising at least about 15 contiguous nucleotides of a DNA molecule according to claim 5; and

(b) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting *M. tuberculosis* infection.

21. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the sample with one or more oligonucleotide probes comprising at least about 15 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12; and

(b) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting *M. tuberculosis* infection.

22. The method of claims 20 or 21 wherein the biological sample is selected from the group consisting of whole blood, sputum, serum, plasma, saliva, cerebrospinal fluid and urine.

23. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the biological sample with a binding agent which is capable of binding to a polypeptide according to any one of claims 1-4; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting *M. tuberculosis* infection in the biological sample.

24. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the biological sample with a binding agent which is capable of binding to a polypeptide having an N-terminal sequence selected from the group consisting of sequences provided in SEQ ID No: 129 and 130; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting *M. tuberculosis* infection in the biological sample.

25. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the biological sample with a binding agent which is capable of binding to a polypeptide encoded by a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 3, 11 and 12; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting *M. tuberculosis* infection in the biological sample.

26. The method of any one of claims 23-25 wherein the binding agent is a monoclonal antibody.

27. The method of any one of claims 23-25 wherein the binding agent is a polyclonal antibody.

28. A diagnostic kit comprising:

(a) one or more polypeptides according to any of claims 1-4; and

(b) a detection reagent.

29. A diagnostic kit comprising:

(a) one or more polypeptides having an N-terminal sequence selected from the group consisting of sequences provided in SEQ ID No: 129 and 130; and

(b) a detection reagent.

30. A diagnostic kit comprising:

(a) one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 3, 11 and 12; and

(b) a detection reagent.

31. The kit of any one of claims 28-30 wherein the polypeptide(s) are immobilized on a solid support.

32. The kit of claim 31 wherein the solid support comprises nitrocellulose, latex or a plastic material.

33. The kit of any one of claims 28-30 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

34. The kit of claim 33 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

35. The kit of claim 33 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

36. A diagnostic kit comprising a first polymerase chain reaction primer and a second polymerase chain reaction primer, the first and second primers each comprising at least about 10 contiguous nucleotides of a DNA molecule according to claim 5.

37. A diagnostic kit comprising a first polymerase chain reaction primer and a second polymerase chain reaction primer, the first and second primers each comprising at least about 10 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12.

38. A diagnostic kit comprising at least one oligonucleotide probe, the oligonucleotide probe comprising at least about 15 contiguous nucleotides of a DNA molecule according to claim 5.

39. A diagnostic kit comprising at least one oligonucleotide probe, the oligonucleotide probe comprising at least about 15 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12.

40. A monoclonal antibody that binds to a polypeptide according to any of claims 1-4.

41. A polyclonal antibody that binds to a polypeptide according to any of claims 1-4.

42. A fusion protein comprising two or more polypeptides according to any one of claims 1-4.

43. A fusion protein comprising one or more polypeptides according to any one of claims 1-4 and ESAT-6 (SEQ ID No. 99).

44. A fusion protein comprising a polypeptide having an N-terminal sequence selected from the group of sequences provided in SEQ ID Nos. 129 and 130.

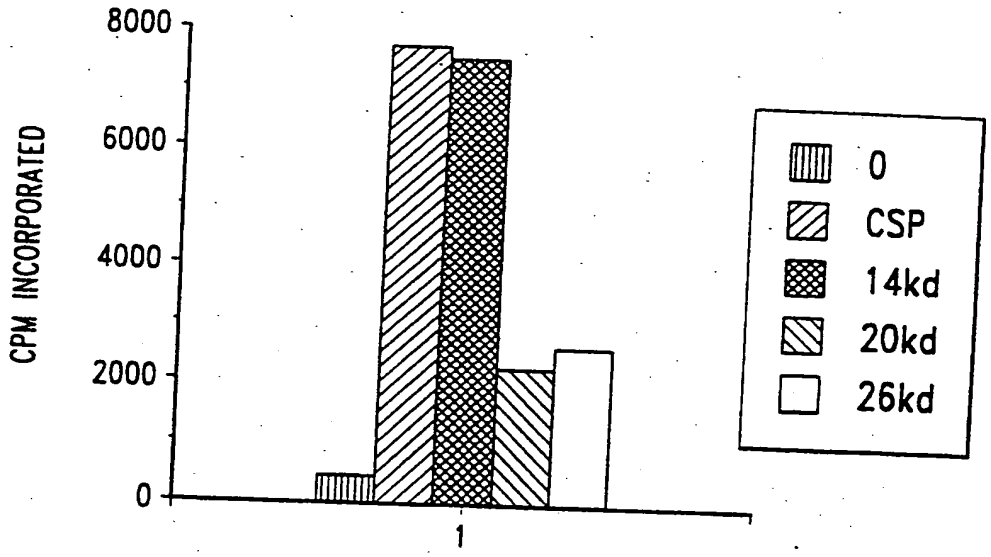

Fig. 1A

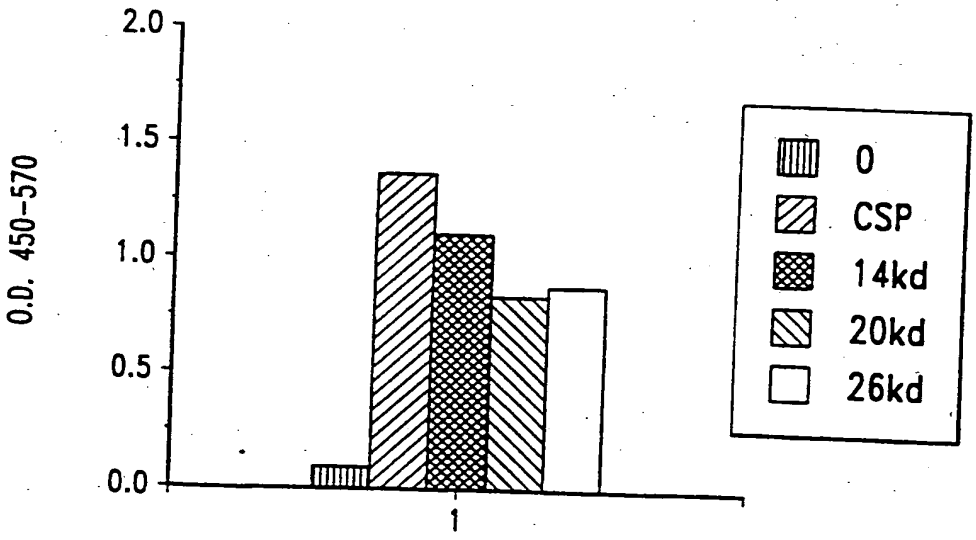

Fig. 1B

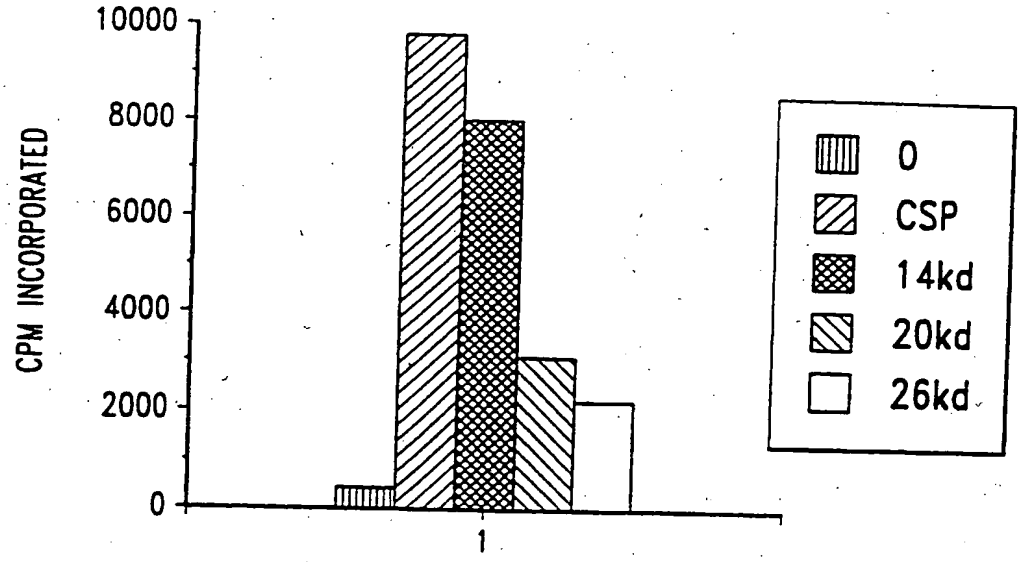

Fig. 1C

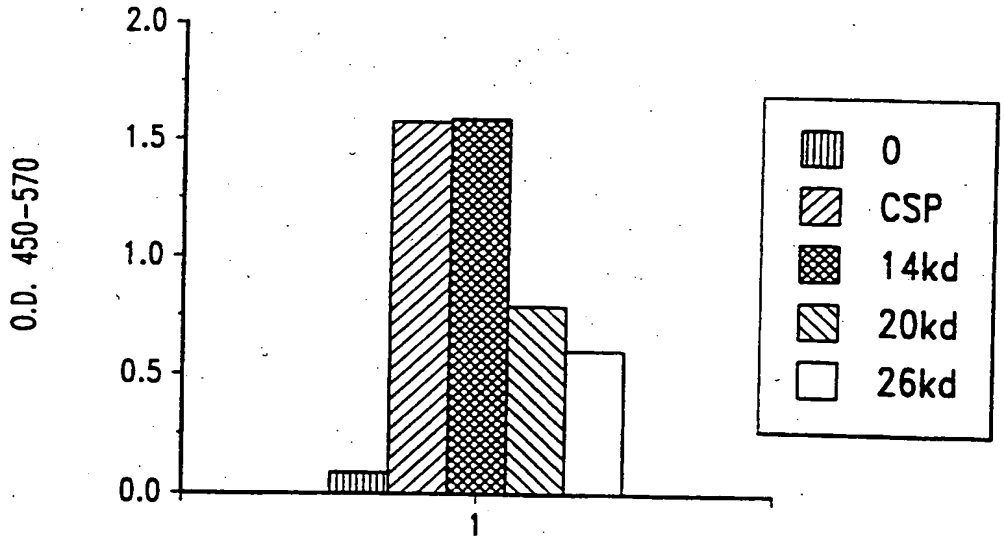

Fig. 1D

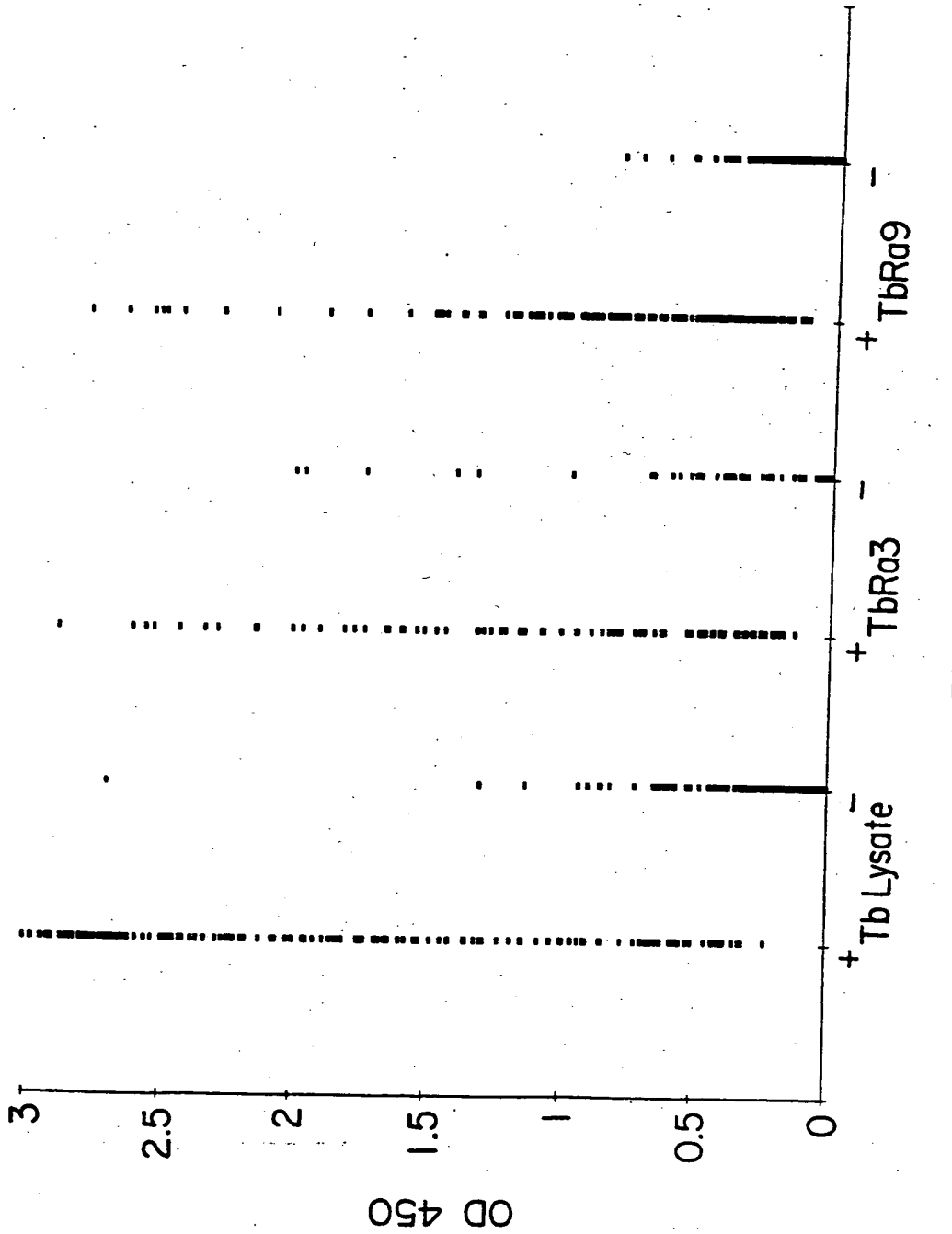

Fig. 2

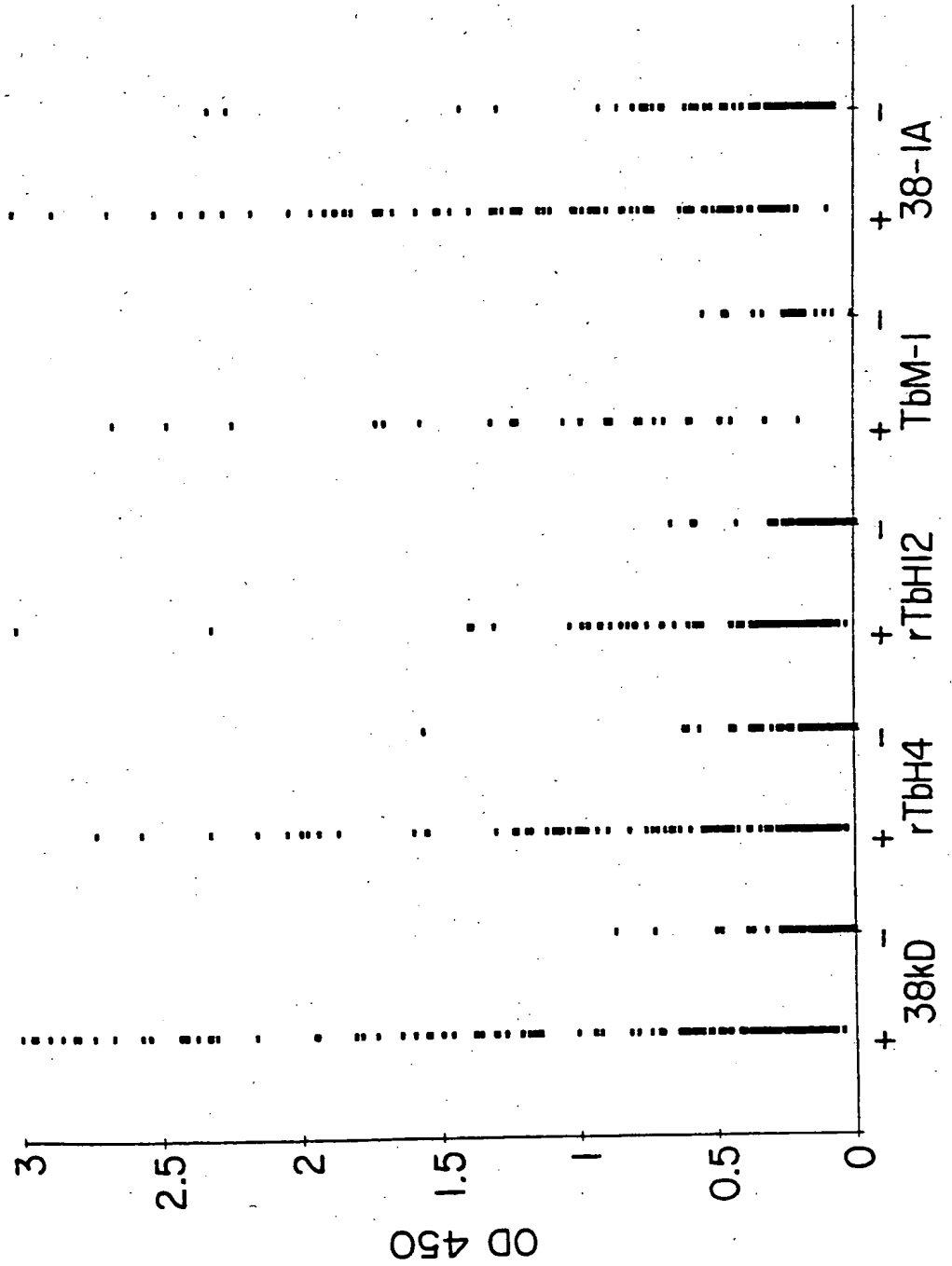

Fig. 3

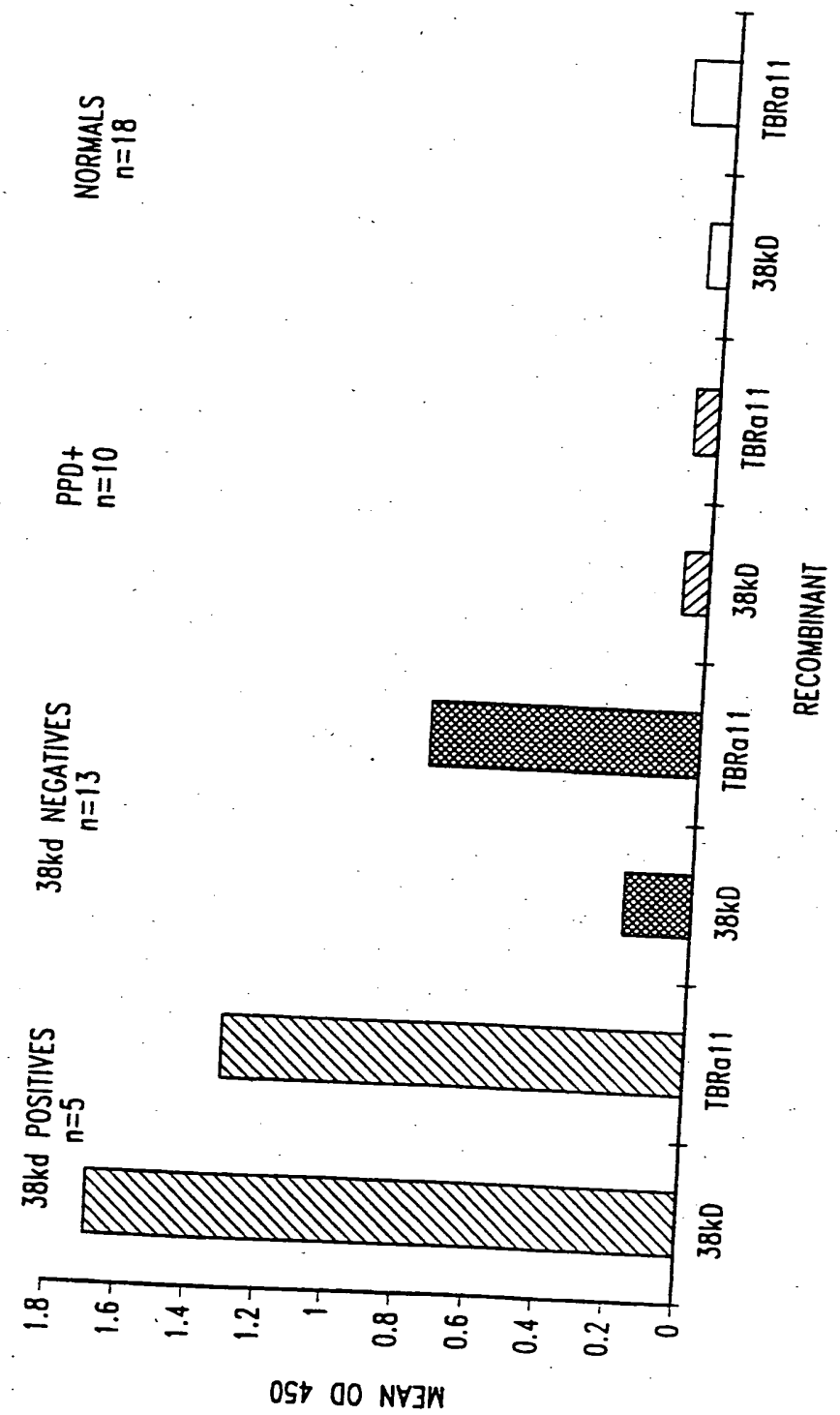

Fig. 4

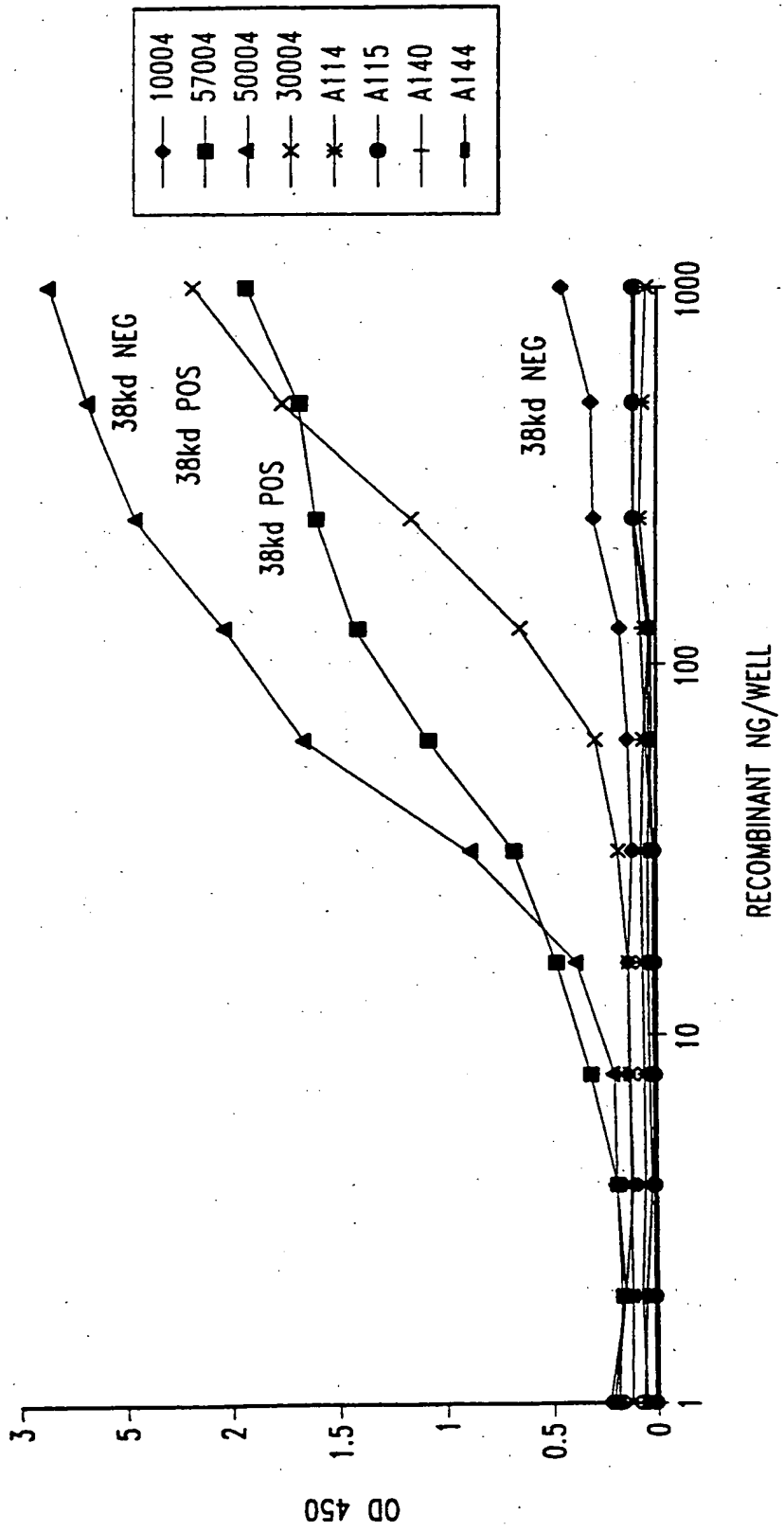

Fig. 5

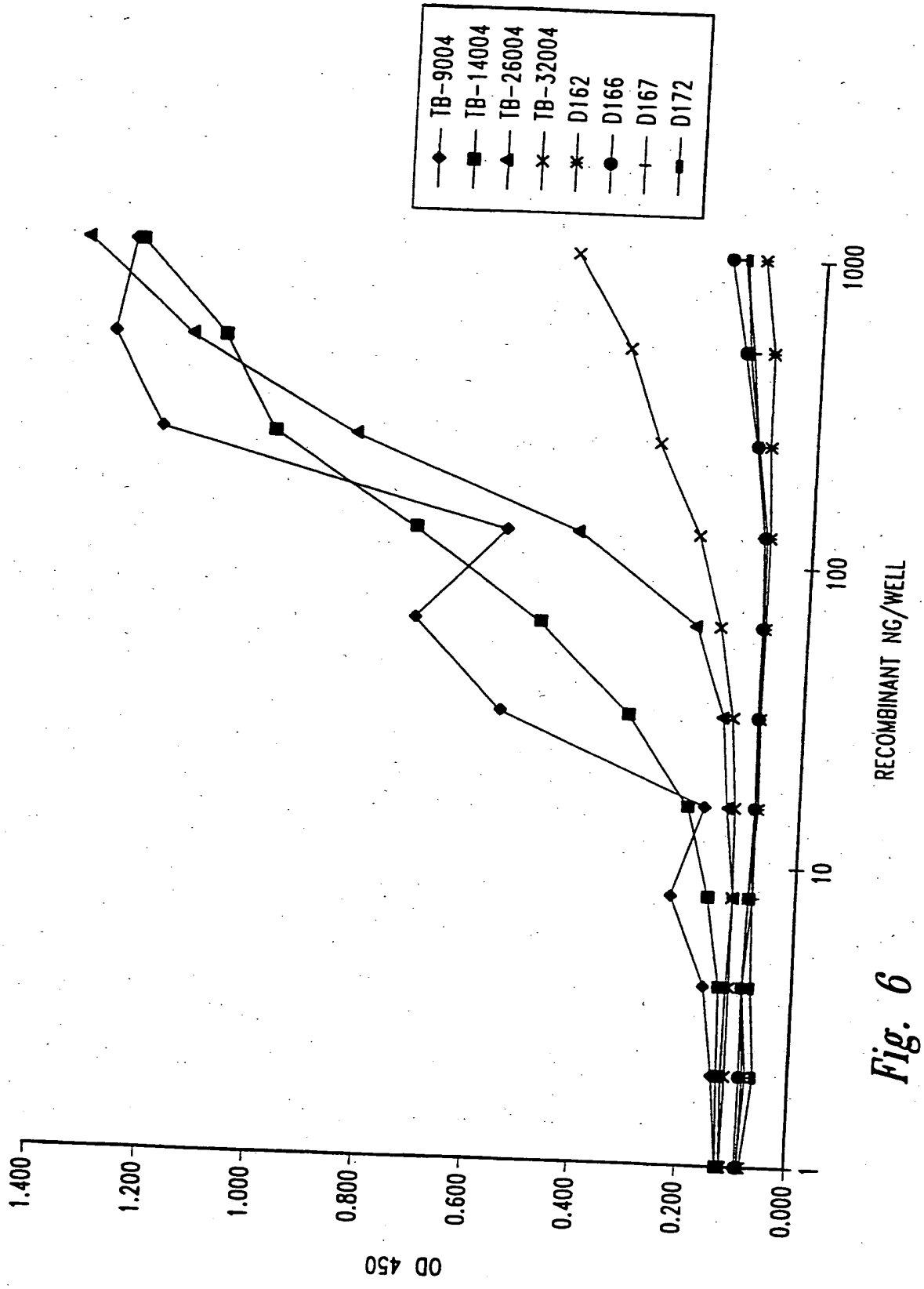

Fig. 6

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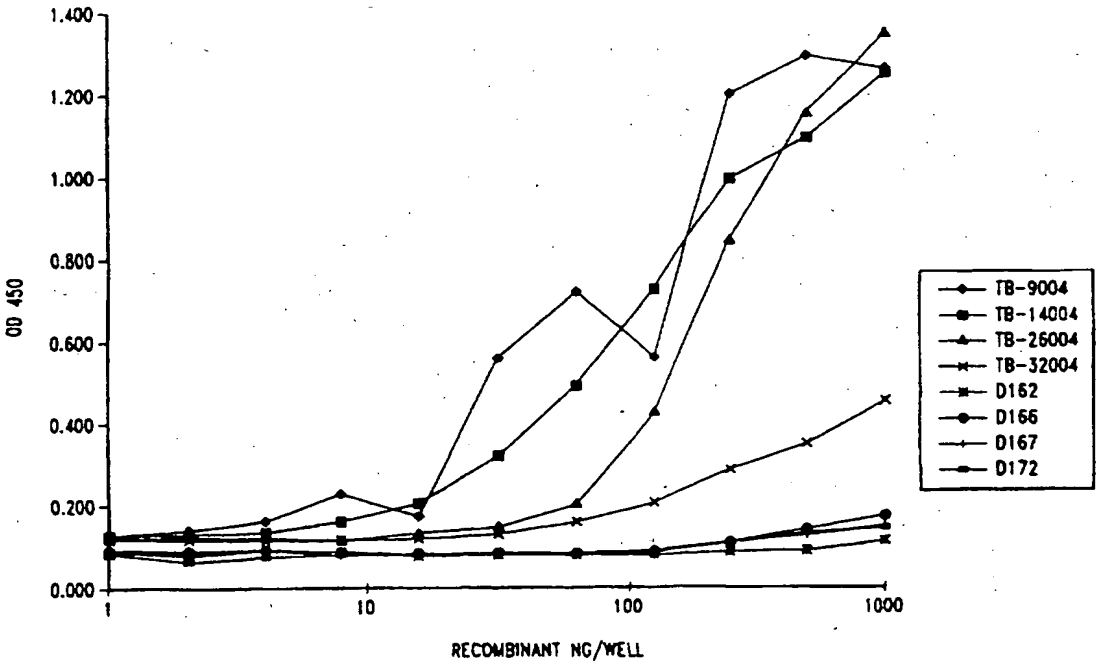

(57) Abstract

Compounds and methods for diagnosing tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one antigenic portion of one or more *M. tuberculosis* secretory or non-secretory proteins, and DNA sequences encoding such polypeptides. Diagnostic kits containing such polypeptides or DNA sequences and a suitable detection reagent may be used for the detection of *M. tuberculosis* infection in patients and biological samples. Antibodies directed against such polypeptides are also provided.

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INTERNATIONAL SEARCH REPORT

Intern al Application No
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CATION OF SUBJECT MATTER
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C12N C07K G01N

n searched other than minimum documentation to the extent that such documents are included in the fields searched

a base consulted during the international search (name of data base and, where practical, search terms used)

ENTS CONSIDERED TO BE RELEVANT

Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
WO 95 01440 A (STATENS SERUMINSTITUT ;HASLOEV KAARE (DK); ANDERSEN AASE BENGAARD) 12 January 1995 see abstract see page 1, line 1-30 see page 4, line 8-31 see page 6, line 22 - page 7, line 21 see page 11, line 18 - page 12, line 31 see page 17, line 8-24 see page 24, line 18-25; figure 1 see page 36 - page 43; examples 2-5 see claims --- -/--	1,3-9, 12,15, 19,20, 28,31,32

her documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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e actual completion of the international search	Date of mailing of the international search report
3 March 1997	04. 06. 97
mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Macchia, G

A/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 01441 A (STATENS SERUMSINSTITUT ;ANDERSEN PETER (DK); ANDERSEN AASE BENGAAR) 12 January 1995 see abstract see page 9, line 3 - page 12, line 24 see page 21, line 14 - page 36, line 4 see claims	1,3-9, 17,20, 23,26, 28,36, 38,40,43
A	EP 0 419 355 A (INNOGENETICS NV) 27 March 1991 see abstract see page 2, line 1 - page 3, line 42 see page 6, line 30 - page 7, line 34 see page 17, line 30 - page 28, line 34 see claims	1,3-9, 13-17, 19,20, 22,23, 26-28, 31-36, 38,40,41
A	INFECTION AND IMMUNITY, vol. 57, no. 8, August 1989, pages 2481-2488, XP002026677 ANDERSEN AND HANSEN: "Structure and mapping of antigenic domains of protein antigen b, a 38,000-molecular-weight protein of mycobacterium tuberculosis" cited in the application see the whole document	12
A	INFECTION AND IMMUNITY, vol. 57, no. 1, January 1989, pages 283-288, XP002026408 YAMAGUCHI ET AL.: "Cloning and characterization of the gene for immunogenic protein MpB64 of mycobacterium bovis BCG"	
A	ANN. INST. PASTEUR/MICROBIOL., vol. 136B, 1985, pages 235-248, XP002026409 ROMAIN ET AL.: "Preparation of Tuberculin antigen L"	
A	WO 92 21758 A (PASTEUR INSTITUT) 10 December 1992	
1 A	AUSUBEL ET AL.: "Current Protocols in Molecular Biology" 1993 , WILEY & SONS , US, NEW YORK XP002026411 see page 10.19.1 - page 10.19.12	

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INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 96/14675

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INFECTION AND IMMUNITY, vol. 55, no. 6, June 1987, pages 1421-1425, XP002026410 YOUNG ET AL.: "Screening of a recombinant mycobacterial DNA library with polyclonal antiserum and molecular weight analysis of expressed antigens" ---	
A	WO 94 00493 A (KAPOOR ARCHANA ;MUNSHI ANIL (US)) 6 January 1994 -----	

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 96/ 14675

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

51 inventions * see continuation-sheets *

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,3-9,12-17,19-20,22,23,26-28,31-36,38,40-43 all partially

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

1) claims 1, 3-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
a polypeptide comprising an antigenic portion of a soluble M. tuberculosis antigen or a variant, having an N-terminal aminoacid sequence as in Seq. ID:115, a DNA molecule encoding said polypeptide as in Seq. ID:96, overlapping or adjacent DNA molecule as in Seq. ID:31, 32, 33, 51 and encoded polypeptides, fusion proteins comprising said polypeptides, an expression vector comprising said DNA molecules, an host transformed with said expression vector, their use for detection of mycobacterial infection in biological samples.

2) claims 1, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:116.

3) claims 1, 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:117 and 25.

4) claims 1, 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:118 and 24.

5) claims 1, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:119.

6) claims 1, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:120.

7) claims 1, 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:121 and 52.

8) claims 1, 5-9, 11-23, 25-28, 30-43 all partially:
same as invention 1 but for Seq. ID:122 and 3.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

9) claims 1, 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:123, 94, 1 and 21.

10) claims 1, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:131.

11) claims 2, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:124.

12) claims 2, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:132.

13) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:2.

14) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:4 and 17.

15) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:5, 14 and 18.

16) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:6.

17) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:7.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

18) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:8.

19) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:9.

20) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:10 and 13.

21) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:15.

22) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:16.

23) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:19.

24) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:20.

25) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:22.

26) claims 3, 5-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:23.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

27) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:26.

28) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:27.

29) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:28.

30) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:29.

31) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:30.

32) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:34.

33) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:35.

34) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:36.

35) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:37.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

36) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:38.

37) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:39.

38) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:40.

39) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:41.

40) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:42.

41) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:43 and 44.

42) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:45.

43) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:46.

44) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:47.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

45) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:48.

46) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:49.

47) claims 4-9, 12-17, 19-20, 22, 23, 26-28, 31-36, 38, 40-43 all partially:
same as invention 1 but for Seq. ID:50.

48) claims 11-16, 18, 19, 21, 22, 25-27, 30-35, 37, 39 all partially:
use of Dna of Seq. ID:11 or of its encoded polypeptide for the detection of mycobacterial infection.

49) claims 11-16, 18, 19, 21, 22, 25-27, 30-35, 37, 39 all partially:
same as invention 50 but for Seq. ID:12.

50) claims 10, 12-16, 24, 26, 27, 29, 31-35, 44 all partially:
use of polypeptide of Seq. ID:129 for the detection of mycobacterial infection.

51) claims 10, 12-16, 24, 26, 27, 29, 31-35, 44 all partially:
same as invention 52 but for Seq. ID:130.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...al Application No
PCT/US 96/14675

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9501440 A	12-01-95	AU 7068694 A	24-01-95
		EP 0749486 A	27-12-96
WO 9501441 A	12-01-95	AU 7068894 A	24-01-95
		CA 2165949 A	12-01-95
		EP 0706571 A	17-04-96
EP 0419355 A	27-03-91	AU 6414390 A	18-04-91
		CA 2042016 A	20-03-91
		JP 4501811 T	02-04-92
WO 9221758 A	10-12-92	FR 2677365 A	11-12-92
		CA 2110389 A	10-12-92
		EP 0589943 A	06-04-94
		JP 6508513 T	29-09-94
WO 9400493 A	06-01-94	US 5330754 A	19-07-94
		AU 4651193 A	24-01-94
		EP 0649435 A	26-04-95
		JP 7508649 T	28-09-95
		US 5559011 A	24-09-96